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Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

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BIOTECHNOLOGY

Managing the Risks of Field Testing Genetically Engineered Organisms

GAO/RCED-88-27

GAO

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Economic Development Division

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The Honorable John D. Dingell
Chairman, Subcommittee on Oversight
and Investigations
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

As requested, this report discusses federal risk management policies and procedures applicable to field testing genetically engineered organisms. The report contains recommendations to the Administrator of the Environmental Protection Agency and to the Secretary of Agriculture to improve regulatory coverage. This is the second report related to biotechnology research and development prepared for the Subcommittee. Our first report, entitled Biotechnology: Analysis of Federally Funded Research (GAO/RCED-86-187), was issued in August 1986.

As arranged with your office, we will make no further distribution of this report until 30 days from the date of this letter. At that time, we will provide copies of the report to the Administrator, Environmental Protection Agency; the Secretary of Agriculture; and the Secretary of Health and Human Services. We will also make copies available to others upon request.

This report was prepared under the direction of Sarah Frazier Jaggar and Flora Milans, Associate Directors. Major contributors are listed in appendix VII.

Sincerely yours,

J. Dexter Peach

J. Dexter Peach
Assistant Comptroller General

Executive Summary

Purpose

The Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, requested that GAO review the federal risk management of genetically engineered organisms intended for agricultural and health uses in the environment. This report (1) evaluates the scope of regulatory policies applicable to deliberate, small-scale releases, (2) reviews the administrative procedures for implementing these policies, and (3) identifies technical methods available to control and monitor risks posed by field testing. It focuses on agencies directly responsible for regulating environmental introductions: the Department of Agriculture (USDA), the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA).

Background

Genetic engineering using recombinant DNA (deoxyribonucleic acid) techniques, first developed in the mid-1970s, is a method for combining genetic material from widely different as well as closely related organisms. It allows the construction of organisms with new combinations of traits more precisely and rapidly than is possible by using traditional processes, such as plant breeding. It promises a broad range of applications, including increasing agricultural production, controlling agricultural pests, cleaning up pollution, and immunizing against contagious diseases.

Scientists have compared the environmental effects of releasing genetically engineered organisms with past introductions of nonindigenous organisms (naturally occurring organisms placed in environments where they are not native). Although releases of nonindigenous organisms were considered unlikely to cause disruptions, adverse consequences have occurred and, in some cases, have been substantial. Predicting and managing the risks of environmental releases of genetically engineered organisms requires an understanding of the organisms' ability to survive, multiply, and spread; their potential to transfer genetic material to other organisms; and the type and extent of harm they may cause.

Results in Brief

USDA, EPA, and FDA have limited experience with genetically engineered organisms used in the environment and are uncertain about their effects. Each agency generally uses a detailed prerelease evaluation process that draws upon a broad range of scientific expertise to review proposals for field tests on a case-by-case basis.

The agencies have made efforts to coordinate their policies and review procedures. USDA has issued a new rule and EPA is considering amending

regulations to cover the range of products under their jurisdictions more completely. Even so, some organisms are not subject to regulation due to differences in legislative mandates and risk management policies.

Although genetically engineered microorganisms cannot be completely contained at the field-test site, a variety of control methods are available to limit their dispersal and impact. These include setting physical barriers at the test site and selecting organisms with vulnerable biological features. Choosing the appropriate degree of control involves a tradeoff between minimizing risk and maximizing the realism, and therefore the usefulness, of the field test.

GAO's Analysis

Regulatory Policies

In response to concerns about environmental introductions of genetically engineered organisms, federal agencies developed a "Coordinated Framework for the Regulation of Biotechnology," outlining policies and procedures for overseeing environmental use of these products. The principal regulatory tool for managing the risks of field testing genetically engineered organisms is the authority to require permits or other types of approval before release.

Because no statutes specifically target the regulation of genetically engineered organisms, the agencies are, for the most part, applying existing laws that are based on the purposes for which the products are to be used, such as use as pesticides and vaccines. This approach allows genetically engineered organisms to be regulated similarly to those developed by traditional genetic techniques.

The agencies' general policy is to follow a case-by-case approach in reviewing proposed field tests. This prudent approach can allow them to accumulate experience in evaluating organisms and eventually develop generic regulations. However, USDA and EPA are exempting certain categories of organisms from regulatory scrutiny prior to developing scientific information on the behavior of these organisms in the environment.

- USDA exempts from regulation microorganisms formed by transferring certain kinds of well-defined genetic material from plant pests to nonplant pests. Leading scientific associations note that such transfers

could change the organism's ability to compete in the environment and argue for subjecting them to regulatory review prior to field testing.

- EPA has assigned genetically engineered microorganisms to categories on the basis of their presumed potential for harm. Under the Toxic Substances Control Act, microorganisms categorized as less risky are exempt from effective regulatory scrutiny. Although EPA may require submission of an abbreviated prerelease report for monitoring purposes, the agency would be precluded from readily intervening to delay the field test, should questions of safety arise in reviewing the report.

Administrative Procedures for Managing Risk

The agencies are using a preventive approach to risk management. Each proposal to release genetically engineered organisms is evaluated for its potential risk along with measures to be taken to ensure that the risk does not exceed acceptable levels. Prerelease evaluations involve assembling the available data for a particular proposal and applying the judgment of a group of qualified scientists to determine whether the field test should be allowed and under what control constraints. Agency reviews have tended to emphasize risks with limited attention given to potential benefits at the field-testing stage.

The agencies require specific types of data and have the flexibility to request additional data as needed. Their scientific advisory groups reflect a wide range of relevant disciplines and may include officials from other federal regulatory agencies and state governments. Agency approvals are contingent upon specific field conditions and other requirements, such as providing security at the site, implementing waste disposal procedures, monitoring the test organism, and planning for contingencies. They generally require plans for mitigating any unexpected harm and possess the authority to terminate the experiment if necessary. (See ch. 3.)

Technical Methods for Risk Management

Techniques available to control the spread of genetically engineered organisms from the test site vary widely with the type of organism. Genetically engineered plants can be contained by preventing pollen release or seed production or release. However, with microorganisms, complete containment is not achievable so scientists recommend the use of multiple control methods. Designing self-limiting features into microorganisms might prove to be an effective control technique, but scientists do not agree that all such methods will be broadly applicable.

Monitoring is needed to track the success of containment measures and, if necessary, to trigger mitigation actions. However, because a microorganism population can drop below detectable levels and then grow again, even the best monitoring cannot guarantee elimination of the genetically engineered organism. Although some newer monitoring methods for microorganisms can identify particular strains very specifically, they are often slower, more complicated, and less sensitive to low concentrations than certain traditional methods. (See app. I.)

Recommendations

Given the agencies' limited experience in reviewing proposals to field-test genetically engineered organisms and the potential risk associated with their release, GAO recommends some modifications to agency policies in order to narrow gaps in regulatory coverage. GAO recommends that EPA ensure that it has the ability to take effective regulatory action by making all microorganisms covered by the Toxic Substances Control Act subject to premanufacture notice or "significant new use" rule requirements. GAO also recommends that USDA strengthen its regulations under the Federal Plant Pest Act by not exempting from prerelease review those microorganisms created by transfer of a certain type of genetic material. (See ch. 2.)

Agency Comments

USDA, EPA, and the Department of Health and Human Services (HHS) commented on a draft of this report. EPA indicated that it is familiar with the criticism of its Coordinated Framework policy statement and noted that it intends to address these issues in its forthcoming proposed rules.

USDA stated that GAO's study provides a valuable analysis of the procedures used by agencies to regulate field tests of genetically engineered organisms. However, the agency rejected GAO's recommendation as unnecessary, given "the limited nature of the exemption." GAO continues to believe its recommendation is valid because the scientific basis for exempting from review certain genetically engineered organisms released into the environment has not yet been established. (See ch. 2.)

HHS pointed out several areas of disagreement, including GAO's characterization of genetic engineering, the extent of relevant agency experience, the concept of "case-by-case" review, and GAO's recommendations to USDA and EPA. GAO added material as appropriate to clarify certain positions. However, GAO disagrees with many of HHS' comments and thus has not changed its conclusions and recommendations. (See ch. 2 and app. VI.)

Contents

Abbreviations

AGS	Advanced Genetic Sciences, Inc.
APHIS	Animal and Plant Health Inspection Service
BSAC	Biotechnology Science Advisory Committee
BSCC	Biotechnology Science Coordinating Committee
BTI	BioTechnica International
DDT	dichloro-diphenyl-trichloro-ethane
DNA	deoxyribonucleic acid
EBC	Environmental Biosafety Committee
EPA	Environmental Protection Agency
EUP	environmental use permit
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPPA	Federal Plant Pest Act
GAO	General Accounting Office
HHS	Department of Health and Human Services
IBC	Institutional Biosafety Committee
IND	investigational new drug
NAS	National Academy of Sciences
NIH	National Institutes of Health
NIH-RAC	NIH's Recombinant DNA Advisory Committee
OPP	Office of Pesticide Programs
OTS	Office of Toxic Substances
PPQ	Plant Protection and Quarantine
PQA	Plant Quarantine Act
RCED	Resources, Community and Economic Development Division
rDNA	recombinant deoxyribonucleic acid
SPW	Shackelton Point Workshop
TSCA	Toxic Substances Control Act
USDA	Department of Agriculture
VSTA	Virus-Serum-Toxin Act

Chapter 1

Introduction

The prospect of using genetically engineered organisms in the environment has stirred debate about the magnitude and kind of potential risk involved. Because the new products are living things that may multiply and spread, there is concern that any problems resulting from their use may be difficult or impossible to correct. (By contrast, chemicals do not multiply and therefore seem more manageable and their effects, more predictable.) Proposals to field-test genetically engineered organisms have raised questions about whether such activities could harm public health or the environment and whether current federal regulations provide for adequate oversight.

To maintain public confidence and continued technological development, a sound risk management system is essential. Control measures are available and can be required as part of the regulatory process to minimize the probability of harm. This report discusses the laws, policies, administrative procedures, and control methods—components of a risk management system—used by federal regulatory agencies to protect public health and the environment from potential risks associated with releases of genetically engineered organisms.

Background

"Genetic engineering," as used in this report, refers to the new technologies developed in the last 15 years that involve the direct manipulation of the genetic material of plants, animals, and microorganisms. These technologies, such as recombinant DNA[1] (rDNA), increase our ability to produce materials that are difficult to obtain by older techniques, as well as our ability to construct novel strains of organisms. In this way, genetic engineering can expand and improve on the traditional methods of applied genetics in health, agriculture, and industry.

The use of genetically engineered organisms in the environment offers commercial opportunities in a broad range of applications. At the same time, they generate difficult questions for federal regulators uncertain about the safety of field testing. Agencies are faced with the complexity of deciding whether and how to regulate releases before exposure occurs and possible hazards are identified. They must contend with the twin objectives of allowing society to benefit from new products and minimizing risks to public health and the environment.

[1]Recombinant DNA (deoxyribonucleic acid) processes refer to recombining or splicing segments of the genetic material, the DNA, of one organism into the DNA of another and having that recombined material reproduced in the offspring.

Applications of Genetic Engineering

The use of living organisms made with rDNA techniques is already providing a wide range of benefits to society. Compared with conventional processes (plant breeding or selection of randomly produced mutant microbes), such genetic engineering techniques offer a more precise means of creating many products. They can also dramatically shorten the time required to perform certain biological processes, such as producing new strains of plants and animals. Most strikingly, the new genetic engineering has made it possible to transfer genes between very different kinds of organisms—something not previously achievable. This has allowed, for example, bacteria to be used to produce such products as interferon and human growth hormone.

In the past decade, genetically engineered organisms made by rDNA have come into increasingly wide use in contained systems, such as laboratories and drug manufacturing plants,[2] to generate products. A number of different types of genetically engineered organisms are now being considered for use in the environment. Possible commercial uses for these organisms include increasing agricultural production, controlling agricultural pests, processing foods, immunizing humans and animals against disease, recovering metals in mining, producing energy, and controlling pollution.

Genetically engineered microorganisms fall into several groups. Genetically engineered bacteria being tested or considered for field testing include

- plant-inhabiting bacteria modified to help protect crops such as strawberry and potato plants against frost,
- soil bacteria given a gene for a toxin from other bacteria, thus giving them pesticidal activity for use against corn-root cutworms, and
- bacteria engineered to enhance their nitrogen-fixing capabilities and thereby aid the growth of legumes, in this case, alfalfa.

Viruses are a second group of genetically engineered microorganisms proposed for commercial use in the environment. Examples include

- a viral vaccine that not only protects animals from a disease, but makes it possible to distinguish immune from infected livestock in the event of an outbreak, and

[2]As discussed in appendix II, such facilities are relatively contained, but some release of microorganisms occurs routinely.

- viral vaccines produced by adding genes from a disease organism into a carrier virus, for use in immunizing humans against herpes, influenza, hepatitis B, rabies, and AIDS.

Among the genetically engineered plants[2] under development are

- plants modified to resist a tumor-causing disease, crown gall,
- plants given a toxin-producing gene to provide protection against insect pests, such as tobacco hornworm or caterpillars, and
- plants altered to resist the damaging side effects of chemical weed killers, thereby protecting crops and expanding markets for herbicides.

Problems Facing Risk Regulators

At this stage in the development of genetic engineering technology, the risks associated with environmental releases are not always easily identified or quantified. Scientific concern about risks from genetically engineered organisms arises, in part, from the unexpected, detrimental effects of certain nonengineered organisms previously introduced into new environments, such as the gypsy moth, which defoliates trees. Another source of concern is that genetically engineered organisms may be difficult or impossible to control once they are released. More generally, the lack of data to answer questions related to safety contributes to fear and uncertainty over the potential for harm. As stated by the director, Cornell University's Ecosystems Research Center,

> "Ecologists believe that we must consider . . . 'surprise.' This means that there are serious limits to our ability to predict effects, especially indirect effects, from a particular introduction and we must recognize those limits of predictability and manage accordingly. The risks are not fixed ones, which we can ascertain from the beginning and apply to all introductions. A whole spectrum of introductions exists, from benign to potentially dangerous. The challenge is to learn how to manage risks."[3]

In general, federal regulatory authorities have responsibility for identifying the most serious risks early and determining the appropriate degree of control. Hence, another concern in the debate on genetically

[2]The plant most commonly used for these experiments is tobacco, an extremely well-understood and easily controlled organism, long considered the "white mouse" of the plant world for research purposes.

[3]Simon A. Levin, "Appendix E. Workshop Perspective from a University Scientist," in Prospects for Physical and Biological Containment of Genetically Engineered Organisms: The Shackelford Point Workshop on Biotechnology Impact Assessment, October 1-4, 1985, ed. James W. Gillett, Ecosystems Research Center Report No. ERC-11 (Cornell University, March 1987), p. 99.

engineered organisms is the appropriateness of the government's framework for regulating environmental releases. Federal agencies are imposing regulatory requirements for products that have yet to demonstrate harmful effects and are applying these requirements early in the product development process, at the initial field-test stage. Their stated goals are to minimize risk to public health and the environment while supporting industrial productivity and competitiveness.

In addressing the tradeoffs involved in balancing risks and benefits, federal authorities often consider the costs imposed by regulation. Regulation can impose real economic costs in terms of efficiency, international competitiveness, and innovation. Some observers contend that extensive paperwork and containment requirements would divert resources away from beneficial research. Federal officials are concerned that costs of relatively stringent regulation in the United States will offer some foreign competitors a cost advantage to the detriment of U.S. companies. Furthermore, the cost of regulatory compliance may put small firms at a competitive disadvantage and limit the incentive for technical innovation.

Concepts of Risk Assessment and Risk Management

Many regulatory agencies concerned with protecting public health and the environment base their decisions on the risk analysis process. "Risk" is defined as a compound estimate of the likelihood and magnitude of an adverse effect resulting from an event: how probable is it that something adverse will occur, and how bad are the consequences? Through the risk analysis process, hazards are identified, estimated, and evaluated. The process consists of examining information on the level of risk from a particular source, the acceptability of that risk level, and possible actions to reduce the risk, if necessary. In some cases it may lead to a decision to take some risk-reducing action.

The risk analysis process has two elements: risk assessment and risk management. Risk assessment is a scientific estimation of the likelihood and magnitude of threat. Risk management is the pragmatic decision-making process concerned with what to do about the risk (for example, leave it alone or spread it differently through society) and takes many other factors into account. These terms and their interrelationship were discussed in a 1983 report by the National Research Council. According to the Council,

"Risk assessment is the use of the factual base to define the health effects of exposure of individuals or populations to hazardous materials and situations. Risk management is the process of weighing policy alternatives and selecting the most appropriate regulatory action, integrating the results of risk assessment with engineering data and with social, economic, and political concerns to reach a decision."[1]

Some ecologists have expressed concern about the adequacy of the testing methods required to assess the potential environmental impacts of genetically engineered organisms. Because the development of quantitative risk assessment is limited by our present predictive capacity, initial assessments may be accompanied by fairly large areas of uncertainty. This may change, however, with advances in the state of the art in associated techniques. As demonstrated by experience with other potentially risky products, such as pesticides, the levels of uncertainty could decline as methodologies that improve the quality of risk assessment are developed.

By combining experience and test data to estimate risk before genetically engineered organisms are released into the environment, agencies may develop regulations on a prospective basis. However, because not all data needs can be met by performing laboratory and greenhouse tests, agencies may have to operate at a higher level of risk than desirable. For example, the release of certain genetically engineered microorganisms has raised questions as to whether they can outcompete indigenous species and displace other microorganisms. Although the interactions between a genetically engineered product and other microbes can be assessed, in part, through experiments performed in contained facilities under simulated environmental conditions, many scientists believe that, in the final analysis, ecological concerns cannot be resolved without field testing. At the same time, however, a field test to obtain information for assessing the risk of a genetically engineered organism may itself be risky because of the chance of further proliferation of the organism before the test is over.

[1]National Research Council, Commission on Life Sciences, Committee on the Institutional Means for Assessment of Risks to Public Health, Risk Assessment in the Federal Government: Managing the Process (1983).

Phases of Risk Analysis

The components of both elements of the risk analysis process were defined in a September 1987 GAO report that evaluated federal regulation of health risks.[1] The phases of risk assessment are (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization. The last three components of the process--the phases of risk management—are (5) the development and evaluation of risk management options, (6) regulatory decision-making, and (7) monitoring and evaluation.

Risk assessment begins with hazard identification, when the risk source to be analyzed is determined. Dose-response assessment estimates the magnitude of the risk as a function of the degree of exposure to the hazard, often in terms of the probable occurrence of adverse effects. Exposure assessment characterizes the sources of exposure, the routes and concentrations of exposure, the level of exposure for different population groups, and sometimes exposure under different possible regulatory controls. In risk characterization, the information accumulated from the previous phases is brought together to describe the nature of the risk and estimate its magnitude. Uncertainties associated with the information available as well as groups with different exposures or special sensitivities to the substance are considered and weighed. This information, in turn, is fed into the risk management process.

Risk management begins with the development and evaluation of options for controlling the risk, which depend largely on the legislation pertaining to the substance identified as the source of the risk. Regulatory decision-making results in the decision concerning whether to regulate the risk source and, if so, the option to use. Once a final regulation has been issued, risk monitoring and evaluation help ensure that the regulation is implemented and achieves its objectives.

Three Risk Management Approaches

The type of risk management approach that is selected is usually dictated by the type of hazard being evaluated and the agency's legislative authority. The risk management approaches most generally used are (1) risk-only, (2) risk-balancing, and (3) technological control. The risk-only approach characterizes analyses where only the risk is considered relevant in reaching a risk management decision. Risk-balancing considers

[1] Health Risk Analysis: Technical Adequacy in Three Selected Cases (GAO/PEMD-87-14, Sept. 30, 1987).

other factors in addition to risk level, such as the economic costs or benefits of regulation. Technological control relies on the application of the best technologies available to reduce risk.

Risk-Only Approach

Risk-only management considers only the level of risk: the source is to be controlled if the level exceeds one that is deemed acceptable. For example, under the Federal Food, Drug, and Cosmetic Act, the Food and Drug Administration is required to prohibit any food additive able to induce cancer in humans or animals. Known as the Delany clause, this is an extreme type of risk-only approach (it seeks "zero risk"). The quarantining of species not native to the continental United States is another case where benefits are ignored and zero risk is considered the only reasonable level of risk. Some other risk-only regulations more flexibly allow the existence of a risk source rather than simply prohibiting it.

Risk-Balancing Approach

Risk-balancing is the most commonly used risk management approach. Under this approach, the risks of exposure are weighed against other factors such as the costs of control, the benefits of usage, the effect of regulation on the national economy and on particular industries, and other risks. After a decision to take action has been made, risk-balancing is used, at least in part, in determining the stringency of regulation.

One technique in this category is benefit-cost analysis, in which the decisionmaker weighs the costs of control, explicitly and directly, against benefits such as the avoidance of disease, reduction of damage, and other social goods. For instance, the issue of requiring auto manufacturers to install seat belts in all new cars would entail a comparison of the additional consumer cost with the value of reducing injuries.

When benefit-cost analysis is not appropriate, other related techniques are used, such as risk-benefit analysis. This latter approach evaluates health hazards and compares them with benefits, such as the usefulness of a hazardous substance in a given circumstance. One example is the Environmental Protection Agency's decision-making regarding the use of DDT. The agency weighed DDT's liabilities (serious ecological effects) against its benefits (preservation of crops). Because substitute pesticides were available, the risks exceeded the benefits and were judged to be unacceptable.

Finally, risk-risk analysis compares the risks of different technological alternatives for accomplishing a given objective in order to determine

the alternative with the lowest risk. The estimated risks from nuclear power plant accidents have been compared to risks from alternative utility fuel choices, such as foreign oil supplies or coal production and use.

Technological Control Approach

In technological control, the decisions about the stringency of control are determined by the availability of appropriate technology rather than by other means, such as prohibition. For example, some statutes mandate the "best available technology" to reduce the exposure to a level deemed acceptable. Risk management in these circumstances includes determining what technologies are "available" and determining which among those available are "best." As discussed in detail in appendix I, this risk management approach can be applied to field testing genetically engineered organisms by adopting a variety of biological or physical control measures.

Characterizing the Risks of Environmental Introductions

Many scientists from different biological specialties[7] have addressed the issue of risks associated with environmental introductions of genetically engineered organisms. Our review of the scientific literature indicates that the potential consequences are not unique but are comparable to those associated with introductions of nonengineered organisms into a new environment. Most introductions of genetically engineered organisms are expected to cause no health or environmental harm. However, in some cases, the magnitude of the impacts from an introduction may be severe.

Even if only a small fraction of genetically engineered organisms will have serious ecological consequences, it is difficult to predict the likelihood of such an effect for any particular organism. Both ecologists and molecular biologists have asserted that too little is known about what happens to genetically engineered organisms in the environment and, therefore, evaluation of risks requires a case-by-case assessment of the nature and magnitude of possible adverse effects.

[7]These include scientists from the subfields of biology most familiar with rDNA techniques and organisms (molecular biology and molecular genetics) and those from fields most involved in studying populations of organisms and their interactions with the environments (ecology and population biology).

Potential Environmental Hazards

An important point of agreement among scientists is that using rDNA techniques is not itself the source of any unique risk. The risks of introductions arise from the way the organisms may interact with their environments, rather than from their having been genetically engineered. A 1987 National Academy of Sciences (NAS) paper[5] written by a committee composed of biologists from a range of different subfields concluded that

"Assessment of the risks of introducing R-DNA-engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced."

The NAS and other scientific panels have reported that the risks associated with genetically engineered organisms are not unique. Rather, they are expected to be of the same kind as that from introductions of nonengineered organisms and organisms modified by other methods. In some cases the risks may be similar to those posed by organisms produced by conventional techniques, especially genetic variants with parents from the same or closely related species. Even when organisms exhibit hybrid sets of traits from distantly related organisms, scientists have not identified any new adverse ecological consequences.

The purpose of adding, removing, or changing genes is to produce a modified organism in which some part of the parent's properties or behavior has been altered. The key question is whether the new properties give the genetically engineered organism an undesirable competitive advantage over unaltered organisms. Ecologists have noted that the extent to which an engineered organism differs from the parent organism does not necessarily correlate with the magnitude of the impact of such a change. Some contend that an introduced organism that is very similar to those with which it must compete (in terms of tolerance to temperature, moisture level, habitat, etc.) may be more likely to survive than an organism that is very different.

A study by Cornell University research scientists concluded that concerns about environmental effects from releases of genetically engineered organisms are greatest for microorganisms. For genetic modifications that increase an organism's resistance to some natural stress, a major concern is the potential for escape from the usual population controls. This could result in the displacement of resident organisms

[5]National Academy of Sciences, Committee on the Introduction of Genetically Engineered Organisms into the Environment, Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues (1987).

that are particularly important to humans or the rest of the biological community. In addition, in some cases, such as the biodegradation of toxic substances and nitrogen fixation, the purpose of the environmental release is in fact to change ecological processes. These alterations have the potential to cause substantial changes in the composition of biological communities.

A concern associated with genetically engineered plants is the possibility of releasing a new plant that could become a novel noxious weed. Although nearly any plant can become a weed under the right circumstances, scientists warn that engineering superior traits (enhanced insect resistance or draught resistance or the ability to grow on unusual soils) could enable a plant to spread beyond its natural limits imposed by competitors, climate, or soil. The adverse effects that could result include replacing native species, offering new habitats for undesirable insects or microbes, disturbing ecological processes, and intruding into agricultural fields, forests, or waterways.

Analogies to Previous Introductions

In assessing the likelihood of a genetically engineered organism's becoming established in the environment and causing ecological damage, scientists often make analogies to introductions of nonindigenous organisms. Examples of nonnative organisms that have produced ecological damage in their new environments include the house sparrow, starling, gypsy moth, kudzu vine, chestnut blight fungus, and Dutch elm disease fungus. Arguments have been advanced offering generalizations about the effects of introductions of nonnative organisms, but attempts to state a general risk/no risk rule have been refuted by counter examples.

One claim is that although accidental introductions, such as chestnut blight (a fungus from Asia that wiped out American chestnut trees), can be harmful, deliberate introductions are not as troublesome. However, a classic example refutes this assertion: the mongoose was intentionally introduced onto Caribbean islands to control rats in sugar cane fields, but became a great pest that was blamed for the decline of native birds and reptiles. Another claim is that the domestication of organisms has been benign. Examples have included agricultural crops transported between continents—grains from Eurasia to the Americas and corn and potatoes from the Americas to the Old World. However, this generalization is challenged by pointing out that introduced livestock have severely altered plant communities and soils and that plants used as crops in one geographic area can be the most troublesome weeds in another.

The scientific literature that we reviewed indicated an important distinction between instances in which genetically engineered organisms are introduced into a new environment and instances in which they are reintroduced to the environment from which their parent organisms came. According to the NAS committee, the proper analogy for reintroducing genetically engineered organisms into the environment from which they came is the traditional experience in breeding and testing new strains of plants and microbes. This is considered a lower risk situation. In contrast, it indicated that the analogy chosen for introducing genetically engineered organisms into new environments is the previous experience of introducing nonengineered organisms into new environments. Such cases are believed to be of relatively higher risk. However, even for these situations only a small fraction of organisms actually became established, and only a minority of these caused ecological disruption.

One consideration, raised from an ecological view, was not discussed in the NAS paper. Organisms may be given a fitness advantage over indigenous types when purposely modified to overcome a natural limiting factor (such as sensitivity to low temperature or low moisture). This could be all that is necessary for them to spread substantially beyond their original environment and have significant ecological impact.

In summary, scientists believe that the probability of ecological disruption from releases of genetically engineered organisms is low. However, as with introductions of nonindigenous organisms, the magnitude of the impact may be extremely severe. Referring to the record of past introductions, a leading ecologist has warned that "avoidable mistakes were made over and over when species were deliberately released on new lands, because responsible people had oversimplified expectations repeatedly."

Predicting the Risk in Individual Cases

Ecologists have pointed out that, although some proposed introductions can be recognized as too dangerous to permit, there are limits to predictability. No simple predictive laws exist, based on just a few parameters, to determine the effects of any particular introduction. For regulators, a major source of concern is that it may not be possible to identify in advance those rare instances that may have serious consequences. Therefore, as noted in the NAS paper and other scientific reports, case-by-case evaluations of proposed field tests, from an ecological perspective, are recommended.

Among the ecological issues relevant to predicting the potential impacts of an introduction is the fate and movement (the survival, growth, and dissemination) of the organism and its genetic information. In addition, experience in biological control has shown that the scale and frequency of releases are also important in determining ecological consequences. Large-scale or sustained applications may have consequences different from small scale or single applications. Therefore, although individual introductions may present only low risk, the cumulative effect of these cases may raise additional concerns for regulators.

A general framework for examining the risk of specific releases was proposed by a microbial ecologist.[9] It takes the form of the following six questions:

(1) Will the organism be released?

(2) Will it survive?

(3) Will it multiply?

(4) Will it spread to other sites?

(5) Will it be harmful?

(6) Will it transfer genes to other, nontarget organisms?[10] (If so, repeat questions four and five.)

Estimating the risk using these six questions is made difficult by the limitations in the currently available data. The ability to predict the behavior of genetically engineered organisms in the environment was addressed in a January 1986 report by the Study Group on Biotechnology of the Environmental Protection Agency's Science Advisory Board. In describing the state of scientific knowledge, it reported that

"the current data base must be expanded to allow for accurate prediction of which types of organisms will and will not proliferate. . . little information exists on gene transfer in nature. . . there is limited understanding of the traits contributing to successful dispersal."

[9]Martin Alexander, "Ecological Consequences: Reducing the Uncertainties," Issues in Science and Technology, vol. 1, no. 3 (Spring 1985), pp. 57-68.

[10]For example, plants genetically engineered to resist environmental stresses, such as herbicides, may transmit the new trait to weedy varieties of the same or other plants, resulting in resistant weeds that may be harder to control.

Because of these data deficiencies, estimating the probabilities in this six-step framework is the difficult task confronting risk assessors.

The framework also serves well as a guide to risk managers. Risk management for genetically engineered organisms is an effort to prevent damage that may come from proceeding with their release. Administrative actions may require the use of technical methods to lessen the chance of a positive answer to each of the six questions above, thereby reducing the risk of using genetically engineered organisms in the environment.

Objective, Scope, and Methodology

In its letter dated October 10, 1986, the Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, asked us to review the status of federal risk management of genetically engineered organisms used in the environment. The objective of this report is to examine policies and procedures for avoiding or controlling possible undesired effects of environmental releases of organisms intended for either agricultural or health uses.[11]

Depending on the type of product or its purpose, the agencies responsible for regulating these risks are the Department of Agriculture (USDA), the Environmental Protection Agency (EPA), and the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA). Although the National Institutes of Health (NIH) previously had a lead role in reviewing applications for releases of rDNA organisms, it has recently changed its guidelines to allow review and approval by other federal agencies to substitute for its oversight of such experiments.

Early in our investigation of this issue, we found that the primary risk management mechanism available to these agencies is to require that permission be sought prior to conducting field tests. Given this approach, we focused our review on

- examining the scope of laws and regulatory policies applicable to deliberate, small-scale releases to the environment of living, genetically engineered organisms (see ch. 2),
- reviewing the administrative measures developed by these agencies to implement their regulatory policies, including establishing prerelease

[11] For a detailed analysis of the risks associated with environmental releases, their predictability, and other scientific issues related to risk assessment and management, see Office of Technology Assessment, New Developments in Biotechnology — Field-Testing Engineered Organisms: Genetic and Ecological Issues (OTA-BA-350), May 1988.

review procedures and setting conditions for field-test approvals (see ch. 3),
- identifying technological methods available to control or mitigate risks posed by field testing, including the use of selected biological or physical containment measures (see app. I), and
- describing regulations aimed at preventing inadvertent releases of genetically engineered organisms from contained facilities (see app. II).

Our study excluded nonliving products derived by genetic engineering, such as diagnostic kits that use monoclonal antibodies, and biological substances used as replacement hormones, drugs, and vaccines. While other genetic engineering methods may be used to modify living organisms, we focused our inquiry on products developed using rDNA techniques. As discussed in chapter 2, this distinction is particularly relevant to USDA since its regulation of genetically engineered plant pests addresses only those organisms produced with rDNA technology.

In addition, we do not address the subject of environmental releases of naturally occurring organisms into areas where they are nonindigenous. We recognize, however, that such releases may also create hazards. Some of the risk management policies and procedures for genetically engineered organisms apply as well to this subject.

Further, the approaches discussed in this report do not necessarily address all the risk management measures that agencies might consider in regulating the widespread manufacture and use of such products. As scientists have recognized, the problems that might be associated with large-scale introductions of genetically engineered organisms may differ from those of small-scale testing, which was the focus of our review.

According to FDA, genetically engineered organisms in products that it regulates are more likely to enter the environment during the manufacturing process, rather than through the use of the product. However, in the case of certain biologics and foods, organisms could be released intentionally. Agency officials reported that applications for approval of genetically engineered food products were not expected to occur in the near future. Rather, they anticipate receiving a number of requests to approve new vaccines containing live genetically engineered viruses. Therefore, our review focuses on the agency's regulation of human testing of genetically engineered live vaccines.

During the course of this review, we interviewed agency officials to identify existing or planned regulatory and technical approaches to risk

management. We examined policy statements, working documents, and case materials on specific product applications to USDA and EPA (at the time that this study began, FDA had not yet received an application for a living, genetically engineered product). In addition, we conducted interviews and gathered relevant materials to obtain the views of nongovernmental sources on the issues addressed in this report. These included congressional testimony, letters of public comment on proposed regulations, scientific conference proceedings, and research papers. A selected bibliography of source materials is provided in appendix III. Scientists, lawyers, and other specialists outside of GAO reviewed this report, and their comments have been incorporated where appropriate.

Our analysis was performed from October 1986 to October 1987 in conformance with generally accepted government auditing standards. USDA, EPA, and HHS provided official written comments on a draft of this report. These comments are presented and evaluated in chapter 2 and appendixes IV, V, and VI.

Chapter 2

Federal Policy for Regulating Environmental Introductions

Three federal agencies have dominant roles in regulating the use of genetically engineered organisms in the environment: USDA, EPA, and FDA. These agencies have had extensive experience managing risks of products not made by rDNA techniques. USDA regulates many agricultural uses of plants, animals, and microorganisms; EPA manages a wide array of chemicals and also microorganisms used for pesticidal or nonagricultural, commercial purposes; and FDA oversees a wide range of food and health products, including human biologics. Responsibility for reviewing proposals to field-test genetically engineered organisms has generally been assigned to these agencies following existing jurisdictional lines.

The agencies' principal regulatory tool for managing the risks of field testing genetically engineered organisms is the authority to require a permit, license, letter of nonobjection, or other type of approval prior to their release into the environment or use in human subjects. Regulatory authority has been established in numerous federal statutes designed to prevent the occurrence of harm to the environment and public health. Within these statutory frameworks, policies have been developed whereby agency decisions on releases of genetically engineered organisms are to be based on independent, case-by-case analyses. This approach, rather than one based on compliance with previously defined standards, has been adopted because agencies' experience with environmental introductions is too limited to develop standards.

In our review of the laws, regulations, and policies used to manage the risks of environmental releases of genetically engineered organisms, we found that the agencies' regulatory authorities and policies are generally appropriate, but we also found gaps in authority and product coverage. Not all classes or users of genetically engineered organisms in the environment are subject to regulation. In addition, although defining categories of organisms that deserve different degrees of regulatory scrutiny may be reasonable, some agencies have already exempted products from review—an action regarded as premature by certain professional biological associations.

Development of the Coordinated Framework

Regulations governing rDNA research have evolved since the 1970s, from a prohibition on all releases to approval of field tests by the appropriate regulatory agency. In the mid-1970s, in response to concern over the safety of rDNA experiments, the National Institutes of Health's Recombinant DNA Advisory Committee (NIH-RAC) was formed to review genetic engineering research funded by NIH. The first set of guidelines developed for rDNA research, issued in 1976, was primarily focused on preventing

accidental escape of organisms from the laboratory. Among the five types of experiments considered too hazardous to be performed were environmental releases of rDNA organisms. The NIH-RAC gradually relaxed this position and revised its guidelines to remove the prohibition against research involving environmental introductions. Subsequently, the number of proposals to release genetically engineered organisms increased and they included agricultural, environmental, and other issues outside of NIH's biomedical focus. As a result, NIH believed, it was being drawn beyond its traditional responsibilities and sought to reduce its role in reviewing proposals for such research. When field-test proposals were first submitted, NIH invited regulatory agencies to review them. Now most proposals for field tests are reviewed directly by agencies with appropriate jurisdiction.

The federal government's regulatory policy for genetically engineered organisms was coordinated by the Domestic Policy Council (formerly known as the Cabinet Council on Natural Resources and the Environment) Working Group on Biotechnology. This group, consisting of representatives from 18 agencies and executive offices, produced a "Proposal for a Coordinated Framework for Regulation of Biotechnology," published in the Federal Register on December 31, 1984. It presented a matrix outlining the existing regulatory requirements that may be applicable to products containing genetically engineered organisms. It also included a compilation of proposed policy statements that describe how FDA, EPA, and USDA intended to apply their existing regulatory authority to genetically engineered products. In addition, it recommended the establishment of a coordinated science review mechanism to promote consistency in agency risk assessments.

The administration announced in the Federal Register on November 14, 1985, the establishment of the Biotechnology Science Coordinating Committee (BSCC) to assist in sharing information on science issues related to research and commercial development of the technology. Housed in the Office of Science and Technology Policy, BSCC is composed of senior policy officials from USDA, EPA, FDA, NIH, and the National Science Foundation. Its role is to serve as a forum for discussing scientific questions raised in regulatory and research applications, to promote consistency in the development of review procedures and assessments, to facilitate cooperation among agencies on emerging scientific issues, and to identify gaps in scientific knowledge.

According to its chairman, the BSCC has primary responsibility for addressing the scientific questions arising with genetically engineered

organisms, including development and implementation of a risk assessment methodology. However, the BSCC charter does not authorize its involvement in formulating specific agency policies regarding risk management. That responsibility remained with each regulatory agency.

In response to public comments received on the December 1984 proposed Coordinated Framework, agencies such as FDA, EPA, and USDA published revised statements of regulatory policies in the Federal Register of June 26, 1986.[1] FDA proposed no changes in its regulatory policy. EPA's policies under its pesticide law and certain aspects of its chemical control statute were effective immediately. Other parts of EPA's policy under its chemical law do not become effective until the agency concludes its rulemaking process (expected in December 1988). Until that time, EPA has requested voluntary compliance with most of those proposed provisions. Similarly, USDA's policy required some rulemaking for implementation. Its proposed rules concerning plant pests were included in the Coordinated Framework document; final rules were issued on June 16, 1987.

The following are key elements of the Coordinated Framework:

- Because federal laws are product-specific (that is, they regulate certain product uses), similar products will be treated similarly by particular agencies. Also, genetically engineered products will be reviewed in essentially the same manner for safety and efficacy as products obtained by traditional techniques.
- For the most part, existing laws available for the regulation of products developed by traditional techniques will be adequate to address the regulatory requirements for genetically engineered products. However, for certain products, additional regulatory requirements need to be established.
- Agencies are seeking to adopt consistent definitions of those genetically engineered organisms subject to regulation to the extent permitted by their statutory authorities.
- Agencies should use scientific reviews of comparable rigor and will have scientists from each other's staff participate in reviews.

Although the Coordinated Framework provides direction for agency policies, it does not authorize agency action that could not otherwise take place. Each agency may make decisions and issue regulations on the

[1]Office of Science and Technology Policy, "Coordinated Framework for Regulation of Biotechnology," (51 Fed. Reg. 23303-93, June 26, 1986)

basis of its statutory authority. In a ruling on a challenge seeking to set aside the Coordinated Framework, the U.S. District Court for the District of Columbia decided that "while the document is not a model of clarity . . . [its contents] are . . . to guide policy-making, not to regulate. . . . [The framework is] merely a first effort to aid in the formulation of agency policy."[2]

Statutory Authority for Regulation

Although no statutes specifically target the regulation of genetically engineered organisms, agencies contend that, for the most part, existing laws available for the regulation of products developed by traditional techniques will be adequate for regulating genetically engineered organisms. However, because existing statutes were not enacted with the intent to regulate genetically engineered organisms, USDA and EPA have acted to extend regulations to genetically engineered organisms.

All federal agencies are required, under the National Environmental Policy Act, to prepare an analysis before taking a major action that may significantly affect the environment. Agencies first perform a preliminary assessment of the possible consequences of an action to determine whether to prepare an environmental impact statement or a finding of no significant impact. If the environmental assessment indicates a significant environmental impact, the agency must prepare a detailed environmental impact statement.[3] The Coordinated Framework states that an environmental assessment or a broader environmental impact statement may need to be prepared before approving a release of genetically engineered organisms, but this depends on the characteristics of the proposal. EPA's actions under most of its environmental statutes have been considered to be the functional equivalent of National Environmental Policy Act compliance.

For certain products, additional regulatory requirements pursuant to existing statutes are being established. Although USDA's approach follows the agency's authority with conventional products, USDA has issued a final rule to apply its plant pest control laws to products of rDNA technology. The EPA strategy is to regulate genetically engineered microbial products using existing authority with some additional rulemaking for

[2]See Foundation on Economic Trends v. Johnson, 661 F. Supp. 107, 109 (D.D.C. 1986).

[3]Such a statement must describe the environmental impact of the proposed action, any adverse environmental effects that cannot be avoided should the proposal be implemented, alternatives to the proposed action, the relationship between local short-term uses of the environment and the maintenance and enhancement of long-term productivity, and any irreversible and irretrievable commitments of resources that would be involved in implementing the proposed action.

its chemical control statute. Unlike USDA and EPA, FDA does not plan to promulgate new rules for regulation. The most applicable laws of each agency for regulating genetically engineered organisms for agricultural or health-related purposes are discussed in the following section.

Department of Agriculture

USDA's mandate is to protect and enhance agriculture and forestry in the United States. Responsibility for the regulation of genetically engineered organisms at USDA rests with the Animal and Plant Health Inspection Service (APHIS). It administers a variety of statutes enacted to prevent the introduction and spread of animal diseases or plant pests;[1] intentional environmental releases of genetically engineered organisms are regulated under these statutes. Specifically, the Virus-Serum-Toxin Act of 1913 (VSTA) is applicable to the release of genetically engineered organisms that treat or prevent disease in animals. The Federal Plant Pest Act (FPPA) and the Plant Quarantine Act (PQA) provide authority for regulating the movement into or within the United States of genetically engineered organisms that may be plant pests. In its June 26, 1986, policy statement, USDA proposed changes in its regulation of environmental introductions of such organisms. After receiving public comments, it issued a final rule[2] establishing Part 340 of Title 7 of the Code of Federal Regulations, which is highlighted below.

Animal Biologics

Under VSTA, USDA exercises regulatory authority over the importation, exportation, movement, and production of veterinary biological products.[3] Products must be prepared in a USDA-licensed establishment, and each product must be individually licensed for production. To obtain a product license, the applicant must submit data establishing the purity,

[1]A plant pest is "any living stage (including active and dormant forms) of insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, or parasitic plants or reproductive parts thereof; viruses; or any organisms similar to or allied with any of the foregoing; or any infectious agents or substances, which can directly or indirectly injure or cause disease or damage in or to any plants or parts thereof, or any processed, manufactured, or other products of plants." 7 CFR 340.1.

[2]USDA APHIS, "Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There Is Reason to Believe Are Plant Pests," (52 Fed. Reg. 22892-915, June 16, 1987).

[3]Veterinary biological products are "all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live microorganisms, killed microorganisms, and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases of animals." 9 CFR 101.2(w).

safety, potency, and efficacy of the product. Because field testing is considered necessary to meet these safety data requirements, the regulations allow for the shipment of unlicensed biological products for experimental purposes involving a limited number of domestic animals. Approval is conditioned on APHIS' determination that the field-test procedures are adequate to prevent the spread of disease. If the environmental assessment produces a finding of no significant impact, APHIS issues a letter of "authorization to ship [an experimental product] for field trials under controlled conditions . . . for the purpose of gathering additional information in support of a license application for this product . . . ."

Plants and Plant Products

FPPA and PQA are applicable to the release of genetically engineered organisms into the environment if the products present a risk of plant pest introduction, spread, or establishment. The agency has promulgated new regulations to enable it to determine whether the introduction of certain genetically engineered organisms would present such a risk. They state that a product is a "regulated article" if (1) it has been genetically modified by rDNA techniques in which any of the organisms involved[2] belongs to a group of designated pest species that may be injurious to plants or is an unclassified organism or (2) the Deputy Administrator determines or has reason to believe it is a plant pest. On the basis of an evaluation of its plant pest status, the release of certain genetically engineered organisms may be prevented or restricted. Specific conditions are prescribed on separate permits for importation or interstate movement and for release into the environment.

Some environmental groups contend that the scope of USDA's regulatory coverage has significant gaps. While consistent with the limitations of its jurisdiction under FPPA, the agency's approach to regulation has raised concerns about the narrowness of its focus. One point in particular that has drawn criticism is USDA's position, as stated in the Coordinated Framework, that "other genetically engineered organisms that are not plant pests or where there is no reason to believe such organisms are plant pests would not be regulated." The Environmental Law Institute noted that organisms beneficial to plants, which are expected to be the bulk of products to be developed for intentional release into the environment, would not be reviewed or regulated at all. According to the Institute, "there are numerous organisms outside the confines of the plant

[2]The organisms involved include the recipient, the donor, and the source of the vector (the genetic element used to transfer DNA from the donor to the recipient organism).

pest category that are of concern and should be reviewed for environmental impact prior to [release]."

In a memorandum addressing this question, USDA's Office of General Counsel indicated that the agency does have authority under FPPA to regulate genetically engineered plants when their plant pest status is unknown. Moreover, an APHIS official characterized USDA's regulatory coverage of potential genetically engineered plant pests as conservative. USDA reviews not only the types of genetically engineered organisms most likely to be plant pests (ones derived from known pests), but also less likely ones, such as those derived from unknown or unclassified organisms.

Nevertheless, according to the official, the agency does not intend to review all genetically engineered organisms that may be developed from the broad range of groups of organisms that can include plant pests. In explaining the Coordinated Framework statement, he reported that USDA does not have a mandate to examine every genetically engineered organism of the biological groups listed, any more than it is required to review the many new nonengineered organisms that are developed every year. It is agency policy, he noted, to require regulatory scrutiny of genetically engineered organisms only to the extent that similar nonengineered products are to be regulated.

Environmental Protection Agency

EPA operates under a number of statutes designed to protect human health and the environment. The major statutes that EPA relies on for authority to regulate certain genetically engineered microorganisms are the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA). Microorganisms to be used as pesticides are subject to FIFRA, and many microorganisms for general commercial and environmental applications would be regulated under TSCA. A number of critics have questioned the discretionary authority claimed by EPA regarding the applicability of TSCA. Some regulatory analysts anticipate court challenges before clear regulatory authority is established.

EPA's policy statement on microbial products contained several proposals to modify its regulations governing intentional releases. Agency officials expect to announce a formal notice of proposed rulemaking by June 1988 and a final rule in December 1988. In the interim, EPA expects voluntary compliance with most of its Coordinated Framework policy statement. If an imminent hazard arises during the rulemaking period,

the agency believes it could use its authority under section 7 of TSCA to limit or prohibit the activity.

FIFRA Covers Microbial Pesticides

FIFRA prohibits the distribution, sale, and use of pesticides that have not been registered with EPA. The agency must review all data submitted on each microbial pesticide before determining whether it should be registered. The agency has issued guidance to applicants on developing required data, which is being revised to reflect advances in risk assessment techniques for genetically engineered microorganisms. The agency must determine whether the product will cause, or significantly increase the risk of, unreasonable adverse effects to humans or the environment.

To gather product performance and other data necessary for the application, producers may obtain an experimental use permit (EUP) to conduct field studies. Under FIFRA regulations, an EUP is not generally required for certain small-scale uses (involving 10 acres of land or less) of pesticides. However, for genetically engineered microbial pesticides, EPA has decided that small-scale tests should be evaluated for potential risks to determine whether an EUP is required prior to testing. As a result, in 1984, EPA issued an interim policy statement announcing that it should be notified before any field testing of a genetically engineered microbial pesticide. Unless informed by the agency within a specified time that additional information or an EUP is required, the producer may proceed with small-scale field testing without agency approval.

TSCA Covers Nonpesticidal, Nonagricultural Commercial Microorganisms

TSCA was intended by the Congress to serve as a "gap filling" statute for other environmental laws. EPA considers microorganisms and their DNA molecules as "chemical substances" subject to TSCA and therefore uses it to regulate nonpesticidal, nonagricultural commercial uses of genetically engineered microorganisms. The scope of TSCA includes all microorganisms produced for environmental, industrial, or consumer uses, except where they are manufactured, processed, or distributed for use as pesticides, foods, food additives, drugs, cosmetics, or medical devices.

TSCA requires agency review of new chemical substances. EPA has announced in the Coordinated Framework that it plans to intensively review two types of microorganisms under section 5: (1) intergeneric[8]

[8]An intergeneric organism is produced by combining DNA from organisms from more than one genus. A genus is the second level in the biological classification of organisms; it follows the first level, species. The opposite of "intergeneric" is "intrageneric," meaning coming from within the same genus.

combinations, which it considers "new" microorganisms, would be subject to "premanufacture notice" requirements and (2) pathogenic[a] microorganisms, or those derived from pathogens, would be regulated through a "significant new use" rule. Field tests conducted by noncommercial researchers, however, have a statutory exemption from these regulations. Other genetically engineered microorganisms not in these intensively reviewed classes would be exempt from effective regulatory scrutiny. EPA may require abbreviated informational reports prior to their release into the environment, exempt these organisms from regulatory review, or delegate oversight responsibilities to local peer panels.

To comply with premanufacture notice requirements, "new" microorganisms used in commercial research and development that involve environmental release must be reported to EPA at least 90 days prior to such activity. TSCA specifies the information to be provided in premanufacture notices, which includes all test data in the submitter's possession related to the health and environmental effects of the product. If the information submitted is insufficient, and the agency finds that the microorganisms may present an unreasonable risk or there may be significant human or environmental exposure, EPA may limit or prohibit the manufacture or use of the microorganism pending further evaluation. The agency can issue a consent order to require that data from the field test be evaluated by the agency before any further releases. If no action is taken by EPA after 90 days (extendable to 180 days), the new microorganism will be listed on the TSCA chemical substance inventory once it is actually manufactured or imported. Thereafter it can be used by other manufacturers without their having to submit a new premanufacture notice. While the premanufacture notification rule is in the process of being amended to implement this policy, manufacturers or importers are expected to comply voluntarily.

EPA recognized that the definition of "new" microorganisms excludes some potentially risky products from premanufacture review, namely pathogens, which may cause disease in microbes, plants, or animals. Therefore, to supplement its premanufacture notice requirements, EPA may use the "significant new use" provisions of TSCA to require that it be notified before introduction of pathogenic microorganisms into the environment for nonagricultural new uses. This would subject new environmental applications of genetically engineered pathogens to most of the same requirements as premanufacture notices. Until this notification

[a]A pathogenic organism is one capable of causing disease in other living organisms.

requirement is made final through a "significant new use" rule, EPA expects voluntary compliance.

Another amendment announced in the EPA policy statement would modify an existing research and development exemption. TSCA exempts, from both premanufacture notice requirements and the "significant new use" rule, new chemicals manufactured in small quantities solely for commercial research and development purposes. As currently defined, this rule would allow many microorganisms to go unreviewed by EPA for years after initial field testing. However, because microorganisms can reproduce in the environment and may exhibit new traits, EPA is concerned that field tests for research and development could present significant risks. Therefore, EPA intends to amend its rules to specify that field testing of microorganisms does not qualify for a small-quantities exemption. Until the necessary rule changes become final, EPA expects commercial researchers intending to release new microorganisms and engineered pathogens into the environment to voluntarily notify EPA under the premanufacture notification or "significant new use" rules.

Even under the proposed amendments, noncommercial, or purely academic, research and development would remain exempt by statute from these requirements. EPA has noted that NIH-RAC and the USDA Agriculture Biotechnology Research Advisory Committee have jurisdiction over much of this activity, particularly rDNA experiments at institutions receiving federal funds. However, this may leave a gap in regulatory oversight. Although an environmental release experiment conducted at an academic institution receiving any federal monies requires approval from one of the advisory committees, the same experiment performed at an institution independent of federal funds is exempt from review. Since the same safety concern exists for both industrial and academic research, critics from scientific societies and industry have asked that EPA regulate such experiments uniformly. EPA officials have stated that, at this time, the agency does not believe that release experiments not covered by either TSCA regulations or review by one of the advisory committees are likely.

Finally, EPA announced in its June 1986 policy statement that it may promulgate a reporting rule under section 8(a) of TSCA to collect data prior to environmental releases of microorganisms not covered by premanufacture notice or "significant new use" rule requirements. (To address the problem noted above, EPA has stated that it may decide to use section 8(a) to require reporting of environmental releases involving noncommercial uses of genetically engineered organisms.) Under such a

rule, EPA would collect information on production, use, disposal, and environmental effects, for the purpose of tracking environmental releases of microorganisms and determining future regulatory requirements. EPA has not requested that companies voluntarily comply with this proposal during the rulemaking process.

An important weakness of subjecting releases of genetically engineered microorganisms to a TSCA section 8(a) reporting rule is that it has no ready mechanism to require the manufacturer to suspend the field test pending further agency evaluation should a proposed introduction raise concerns about health and environmental effects. This weakness has been identified by the American Society for Microbiology (a biological life sciences society with a membership of over 34,000), the Ecological Society of America (a professional society of ecologists with 6,500 members worldwide), and others. The monitoring function of section 8(a) can contribute to sound risk management only if EPA has the ability to intervene readily in any questionable cases.

For example, the agency may examine a section 8(a) report and determine that there is insufficient scientific information to assure that the genetically engineered organism and the method of testing are environmentally safe. Such a review could raise questions about the microorganism's genetic stability or competitiveness or indicate that specific monitoring is warranted. However, unlike reviews under FIFRA, EPA would not readily be able to require a full evaluation of the risks. To delay the field test while the agency obtains additional data to conduct a full risk assessment, EPA would have to take regulatory action under sections 6 or 7 of TSCA. Agency officials acknowledge, however, that this would be administratively difficult and involve court action. The Environmental Law Institute has cautioned that

"the only way to regulate organisms [subject to TSCA 8(a) reporting] is under existing chemical or imminent hazard provisions of the statute. These provisions are procedurally so burdensome that the agency will find it impractical, except in egregious cases, to follow up on the leads the 8(a) notices provide."

A further difficulty with an 8(a) rule is that small manufacturers and importers are exempt from section 8(a) reporting and recordkeeping requirements under the general statutory exemption standards for small businesses with certain exceptions. EPA believes that its current generic definition of small manufacturer may have to be modified to reflect the size and financial situation of the average biotechnology company. Public comments received by the agency from industry and scientists noted

that this exemption appears inconsistent with EPA's need to develop a data base to assess risks of environmental release.

Since the publication of the Coordinated Framework in June 1986, EPA has reviewed the public comments received in response to its policy statement. It has recognized difficulties with using section 8(a) to regulate genetically engineered microorganisms not covered by premanufacture notice or "significant new use" rule requirements. These include concerns about EPA's capacity to process the data from the large number of 8(a) reports it anticipates receiving. In addition, the agency recognizes that it would be difficult to take regulatory action on 8(a) reports.

To address these concerns, EPA has been examining a number of alternative regulatory options. One approach, discussed in late 1987, is to require a far briefer report on field tests subject to 8(a) or no report at all. However, this would still leave this group of organisms exempt from effective regulatory scrutiny.

Another approach discussed at that time is to establish Environmental Biosafety Committees (EBCs) to participate in overseeing research and development activities. They would be modeled after NIH's Institutional Biosafety Committees, peer review panels established by universities, companies, and other organizations to implement the agency's safety guidelines for rDNA research. The EBCs would supplement EPA reviews of (1) small-scale field tests of microbial pesticides under FIFRA and (2) intergeneric combinations and "significant new uses" of other microorganisms subject to TSCA. Over time, the agency would eventually transfer the review function for certain categories of microorganisms to the EBCs. Issues related to the structure and composition of proposed EBCs are currently under consideration by EPA's Biotechnology Science Advisory Committee.

Food and Drug Administration

FDA's statutory mandate includes the requirement to ensure the safety and effectiveness of a wide variety of genetically engineered products such as food additives, drugs, human biologics,[10] and medical devices. The manufacture and distribution of vaccines for human use are regulated under two statutory authorities: the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. The Public Health Service

[10]A human biologic is "any virus, therapeutic serum, toxin, antitoxin, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of diseases or injuries of man. . . ." 21 CFR 600-680

Act requires that a manufacturer of a biological product obtain licenses for its manufacturing facility and for each product prior to marketing. Both must meet standards designed to ensure the safety, purity, potency, and efficacy of the product. Under the Federal Food, Drug, and Cosmetic Act, the manufacturer of a new vaccine must comply with "current good manufacturing practice" regulations designed to protect the integrity and purity of the product. These include requirements for equipment, personnel, and production and quality controls.

A vaccine may not be marketed unless it has been approved as safe and effective on the basis of adequate clinical investigations. The clinical evaluation process involves three principal phases. Phase 1, the clinical pharmacology stage of testing, is designed to evaluate the toxicity, pharmacological effects, metabolism, and dose-range requirements. These safety tests are generally done on 20 to 80 healthy subjects. Phase 2, the clinical investigation stage, consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on 100 to 200 closely monitored patients. In phase 3, clinical trials are performed on 5,000 to 10,000 patients after effectiveness has been basically established. They are intended to gather additional data on efficacy and adverse effects.

Sponsors of investigations must initially file a Notice of Claimed Investigational Exemption for a New Drug (IND) before beginning human experimentation. Such an exemption allows the sponsor to ship the product interstate solely for investigational use by qualified experts. Before clinical testing of a biologic in humans can take place, the sponsor must provide FDA with information on the manufacture of the biologic, a complete plan of the proposed clinical study, and reports of preclinical testing in the laboratory and in animals.

Step-By-Step and Case-By-Case Review

According to a broad range of scientists and regulators, regulating products in the environmental testing stages, as well as at the time of commercial use, is appropriate, particularly for the early releases of genetically engineered organisms. Scientists and regulators also agree that reviews should be based on the specific intended use of each product, with the information to be analyzed and the expertise to be applied tailored to the individual case.

In general, there is strong support to begin with a cautious regulatory approach, perhaps applying more intensive regulatory scrutiny when a first examination raises questions of particular risk factors. Then later,

after experience is built up from many cases, review rules may be relaxed as more knowledge is accumulated. The rationale for this step-by-step, case-by-case approach is discussed below.

Step-By-Step Review

In the Coordinated Framework, the BSCC recognized that the assessment of a genetically engineered organism's potential risk needs to progress in a step-by-step fashion. This also has been the approach to research in developing products manufactured by traditional techniques. Testing moves from highly contained facilities to progressively lesser containment as the safety and efficacy of the application are determined. The sequence of experiments begins with controlled laboratory conditions before moving to specialized isolation research, such as greenhouse studies, designed to simulate conditions of eventual environmental use. Information developed by investigators in these first two stages is then used to assess the environmental impact under less controlled testing in small and large field trials.

EPA, for one, has recognized that even if an organism is found to have minimal risk associated with its use under carefully controlled circumstances, it may not have the same minimal impact when used under less controlled conditions. As its use expands from research to commercialization, potential risks not previously considered may call for additional regulatory action. In considering limited field testing of a genetically engineered microorganism, EPA has stated that "a step-wise progression that ensures evaluation of data from one stage before proceeding to the next is a careful and prudent approach consistent with good research and development practices."

Case-By-Case Review

Another widely accepted regulatory approach is that, at this early stage, reviews of genetically engineered organisms proposed for release should be conducted on a case-by-case basis. This point was among the key concerns identified at a workshop convened by the American Association for the Advancement of Science and EPA. In its 1985 final report, the Association stated that

"It is . . . premature to attempt development of a general predictive model for assessing the risks of genetically altered organisms. Because of the vast number of biological possibilities for biotechnology products . . . it is not possible to predict potential effects without specific knowledge of a number of important parameters. Thus, experience must be gained first on a case-by-case basis."

In their policy statements, FDA, EPA, and USDA emphasized that risk assessments for genetically engineered organisms should be performed in the context of individual experiments. A rationale given for this approach is that, because of the very recent development of these products, little direct experience is available for evaluating the health and ecological effects of environmental releases. The case-by-case approach enables the agencies to build on experience gained by its review staff in earlier product evaluations and to develop a progressively larger data base. This should allow for more efficient and accurate decision-making in the future.

The case-by-case approach, however, may have its drawbacks. Academic researchers and industry have pointed out that, in the short term at least, it may result in higher costs to the manufacturer and delays in bringing products to market. For the agency, a case-by-case approach may also require more front-end investment in terms of staff and financial resources.

Moving Toward Generic Regulation

EPA and USDA have indicated that, as they gain knowledge and experience from case-by-case reviews, they expect to develop broadly applicable procedures and guidelines. Such a transition to a more systematic risk management approach could enable regulators to make decisions more efficiently. Standardized regulatory requirements may be developed if scientists can identify generic concerns likely to arise with environmental releases or recognize types of organisms or products more or less likely to be problems. Blending in generic standards with the case-by-case approach could exempt certain organisms or product types or uses from regulation or, conversely, prohibit the use of certain products altogether.

An example of applying this process to risk management is the NIH-RAC experience in overseeing rDNA laboratory research. The NIH-RAC began with stringent guidelines, subjecting all rDNA experiments to detailed review and tight controls. At first, it identified certain classes of experiments that were not to be performed at all. Over time, this stringent position was relaxed, as data and experience produced a better understanding of the risks involved. The NIH-RAC, on the basis of case-by-case review, progressively issued exemptions from review for certain types of laboratory research experiments that today cover approximately 90 percent of all experiments involving rDNA. Regulators believe that the progressive relaxation of regulation has resulted in lowering the costs of

compliance for industry, while maintaining adequate laboratory safety standards.

If the NIH-RAC process is taken as a model, generic rules for overseeing environmental releases of genetically engineered organisms would have to be developed over time from case-by-case experience with the actual situation to be regulated. As noted by the American Society for Microbiology,

"We strongly urge that regulation be considered in the context of the extensive experience that has been gained by the successful operation of the NIH-RAC. We should learn from the process used in regulating recombinant DNA research in which the original guidelines were overly cautious and conservative but were deliberately designed to be relaxed quickly as new information permitted . . . . Generally, with regard to federal policy guidelines, we believe that a case-by-case approach should be adopted until more experience and scientific knowledge is developed in this area."

Categories of Organisms Subject to Different Levels of Regulation

In contrast to this experience-based model, some agencies have already made distinctions among classes of organisms for regulatory purposes. EPA and USDA have established categories of genetically engineered organisms to be subject to more or less stringent review, or even be exempted from regulation, depending on certain biological features of how they were engineered. The rationales given for these categorizations are presented in the Coordinated Framework in terms of relative levels of risk. However, critiques by some professional biological associations bring into question the justification for exempting certain categories of organisms.

In the preamble to the Coordinated Framework, the RSCC defined organisms subject to certain types of agency review. Organisms meeting two different sets of criteria were proposed: (1) organisms produced by exchange of genetic material between supposedly more distantly related, intergeneric organisms and (2) organisms for which either the donor or the recipient of the rDNA is classed as pathogenic. Certain genetically engineered organisms not considered to pose an increased risk to human health or the environment were excluded from the definition. These include (1) intrageneric combinations having no pathogen source and (2) intergeneric or pathogenic organisms in which the transferred genetic material contains only "well-characterized noncoding regulatory sequences" (see explanation of this criterion below under USDA).

These categories are defined by the properties and behavior of the source organisms, rather than by that of the genetically engineered products. This approach assumes that the risks of releasing a genetically engineered organism can be predicted on the basis of the nature of its parents. However, ecologists commenting on the Coordinated Framework point out that determining whether a genetically engineered organism behaves in the environment as predicted from its parent organisms cannot be assumed but must be validated through prerelease testing.

In addition, the rationale given for the treatment of some categories is based on a body of experience that appears related, but is not relevant to the circumstances for which the categories are to be applied. As explained by the chairman of the BSCC, the basis for exempting a category of genetically engineered organisms stems, in large part, from particular exemptions developed by the NIH-RAC. However, the NIH-RAC experience is with organisms used in laboratories and fermentation plants, and it is largely aimed at preventing escape into the environment or disabling organisms to limit their ability to survive outside of a contained facility (see app. II).

In contrast, ecologists at Cornell University's Ecosystems Research Center pointed out that genetically engineered organisms intended for release will be designed to survive and function in the environment at least for some period of time. Therefore, generalizations about risk and exemptions from regulation growing out of experience in containment should not be assumed to pertain to the effects of genetically engineered organisms in the environment. They concluded that "the regulatory issues for deliberate releases clearly are fundamentally different than for controlled laboratory situations and the probabilities of ecological side effects are much greater."

Agency Adoption of the Categories

Because the BSCC does not have regulatory authority, it could not establish which genetically engineered organisms require review or how stringent that review should be. It remains up to the individual agencies to apply their own versions of the categories in developing their policy statements. In fact, the categories have been adopted to different extents by USDA, EPA, and FDA, with correspondingly different consequences for their ability to manage potential risks of environmental releases.

Department of Agriculture

In its final rule on regulating genetically engineered plant pests, USDA defines a "regulated article" to exclude genetically engineered microorganisms that are not plant pests and that have had added only genetic material that consists of "well-characterized noncoding regulatory regions." The agency does not base its regulations of genetically engineered organisms in any way on the other two category distinctions, intra/intergeneric or pathogen/nonpathogen.

The distinction underlying the "noncoding regulatory" exemption refers to the fact that only a portion of the DNA in an organism's genetic material actually carries sequences of coded instructions for the order of assembly of proteins, the main structural and functional molecules of living organisms. Other parts of the DNA may give assembly sequence instructions for other nucleic acids or contain information not related to encoding the assembly of any protein or nucleic acid product. But this distinction focuses on parts of the DNA that give what biologists call regulatory signals (that is, signals controlling the frequency or rate of production of a specific gene product) and applies only to segments whose complete nucleic acid sequence is known. In the Federal Register notice announcing the final rule for genetically engineered plant pests, USDA stated that the transfer of well-characterized noncoding regulatory sequences could not enable the resulting organism to make any new material.

When first proposed, this exemption met with scientific criticism from both the Ecological Society of America and the American Society for Microbiology. They pointed out that the manipulation of regulatory genes can cause quantitative and even qualitative changes in an organism's physiology and significant changes in its nature and behavior. In addition, it was noted that many biotechnology projects are seeking to change some aspects of the function of organisms in their environment through changes in regulatory sequences.

Scientists that we contacted from these critical groups pointed out that APHIS' position assumes that the amount of a gene product could not make a difference to the properties of the organism. In contrast, they noted that the development process in multicelled organisms demonstrates the significant role of regulatory genes. Citing a specific case, a university virologist referred to experiments in which the transfer of a noncoding regulatory sequence into an animal virus made it capable of infecting different hosts.

The Ecological Society recommended that the exemption be eliminated, or at least that it be restricted to bacteria and related microbes, since the rationale for the exemption was based on the gene-exchanging behavior of bacteria. The American Society for Microbiology also advised review of at least some genetically engineered microorganisms with introduced regulatory genes. It suggested that prerelease review of regulatory gene transfers include cases in which regulatory genes are transferred to organisms that make potentially harmful or disruptive gene products.

An APHIS scientist stated that the agency knew of no evidence that a transfer of a noncoding regulatory sequence could change the amounts of products made by the existing genes in the recipient organism. Because the letters of public comment on the proposed rule had not presented documentation of experimental evidence to support the critics' views, APHIS did not change its original position on the exemption. In announcing this exemption from regulation, the agency asserted that when well-characterized noncoding genetic material "is placed into a benign recipient microorganism, the recipient will not acquire plant pest traits or become a plant pest." In spite of the scientific criticism outlined above, it concluded, "APHIS believes that the possibility of harmful ecological consequences would not be considered significant."

In sum, exempting transfers of "well-characterized noncoding regulatory sequences" from prerelease review of genetically engineered microorganisms is still a subject of disagreement among scientists. Leading scientific associations have argued that such gene transfers could result in changing the properties or behavior of the recipient microorganisms. In light of these criticisms, USDA's rule to exempt such transfers cannot yet be regarded as adequately supported by available scientific information.

Environmental Protection Agency

Under FIFRA, EPA has proposed using all three of the BSCC definitions, not as a basis to exempt any genetically engineered organisms from regulatory scrutiny, but rather to establish different levels of review for microbial products under its jurisdiction. As explained above, under TSCA, the agency may, in effect, exempt certain classes of organisms from regulatory scrutiny and may only require information reports for them. Under both statutes, genetically engineered microorganisms that are either intergeneric or classified as pathogens are to be given a detailed review before release into the environment. Microorganisms receiving less intense review under FIFRA and little or no review under TSCA are

- intrageneric combinations not classified as pathogens,
- intergeneric combinations formed by adding only "well-characterized noncoding regulatory sequences," and
- intrageneric combinations formed by transfer from a pathogen to a nonpathogen of genetic material consisting only of noncoding regulatory sequences.

Some scientists disagree with the rationales underlying the inter/intrageneric and pathogen/nonpathogen criteria that EPA proposes to use to set varying levels of review. Scientific criticisms of both criteria are presented below.

Intrageneric/Intergeneric Criterion. The rationale for this distinction is based on the contention that intrageneric, genetically engineered organisms are made from organisms presumably more closely related to each other and therefore less likely to present new combinations of traits than intergeneric combinations, which "contain genetic material from dissimilar source organisms." An additional rationale is that organisms within the same genus are more likely to have already exchanged genetic information by natural mechanisms.

This criterion has received strong scientific criticism that, on the basis of current classifications of organisms, it does not provide a consistently dependable measure of potential risk for regulatory purposes. As a result, the Ecological Society of America recommended that all genetically engineered organisms, not just intergeneric ones, be subject to regulatory review and that the intra/intergeneric criterion be used only to determine the level of review to which a proposed product would be first subjected. If a less intense review raised questions about potential environmental risks, then the product could be elevated to more intense scrutiny. (This option exists under FIFRA, as described in ch. 3.) Scientific criticisms of the inter/intrageneric criterion are based on the following three factors.

First, the existing biological classification of organisms is based on characteristics that may or may not have much to do with genetic relatedness. Information developed over the last 20 years is leading to the recognition that existing classifications of organisms are often not good indicators of actual genetic similarity. Using a measure of relatedness based on genetic similarity, one can identify cases in which all the species in one bacterial genus are more closely related than the members of one species from another genus; for another bacterial genus, the members are more distantly related genetically than are all vertebrates.

Second, a leading ecologist and member of the NIH-RAC pointed out that even if present classifications were valid, a small change in some trait may be all that is necessary for an organism to change its role in an ecosystem and possibly harm the environment as a result. An example could be an addition of some modest ability that allows it to use another resource or overcome a natural limit, either of which may allow it to take a dominant role in an ecosystem.

A third criticism contends that this criterion is based on the behavior of bacteria in laboratories, hospitals, and similar controlled environments, but that it should not be presumed valid for natural or other environments into which such genetically engineered organisms are introduced. Those holding this view note that some troublesome weeds have arisen by traditional intrageneric crosses among plants.

Pathogen/nonpathogen Criterion. Pathogens, as mentioned previously, are viruses or microorganisms that can cause disease in other living organisms. The general rule proposed by EPA is that a genetically engineered organism will be subject to greater regulatory scrutiny if it is a member of, or is derived from, a pathogenic species or if it is engineered to contain genetic material from a pathogen.[11]

Both critics and supporters of regulatory policies have pointed out that this pathogen category includes too wide a range of organisms for regulation. Comments submitted for the American Society for Microbiology, for example, note that for an organism to be a pathogen, it must combine a number of traits, determined by an even larger number of genes. Therefore, less intense scrutiny could be applied to transfers of genetic material from pathogens to nonpathogens. Similarly a bacteriologist and vice president for research and development at a biotechnology company stated that

"The evidence is rather persuasive that a deleterious pathogen cannot be formed by genetically modifying a safe microorganism. A pathogen is a problem not because it

[11]Exemptions from this rule include the following: (1) organisms that are derived from a recognized nonpathogenic strain of a species that includes pathogens, (2) organisms derived by transferring a well-characterized, noncoding regulatory region from a pathogen into a nonpathogen, and (3) organisms in competitive, neutral, or cooperative relationships and opportunistic pathogens. (Opportunistic pathogens are microbes that are usually not pathogenic but can be under certain conditions, such as when a host organism's defenses are weakened.) Also, the definition of pathogen does not address the intra/intergeneric distinction. The EPA policy statement shows that both types of genetically engineered organisms must be included in the general pathogen definition. This means that genetically engineered organisms with pathogenic backgrounds are intended to be regulated more closely than others, in that intrageneric as well as intergeneric recombinants will be scrutinized before being released into the environment.

contains a single "patho-gene," but because it contains many genes all finely tuned and integrated, representing natural bacterial selection over many millions of generations. Thus, it is improbable that adding one or two genes to improve a safe microorganism . . . will render that organism dangerous."

This has led many experts to conclude that genetically engineered organisms formed by the transfer of genes from pathogens to nonpathogens need not be scrutinized for pathogenicity[1] nor be subject to particularly stringent review, except when the transferred gene is for a directly toxic or otherwise dangerous product.

Aware of this criticism, EPA, in February 1987, convened a group of experts to discuss which groups of microorganisms pose greater potential risk and should therefore be subject to more intensive regulatory scrutiny. While no new approaches to defining the term have been adopted, the agency is considering this issue in the context of what one official characterized as "the difficult question of how to define a pathogen in a regulatory sense."

Food and Drug Administration

FDA endorsed the BSCC categories, commenting that it believed them to be appropriate for review of microorganisms for environmental or agricultural applications. Statutes establishing FDA's regulatory authority define the products under its jurisdiction. However, except in its evaluation of foods and food additives, for which the pathogen definition is explicitly used, the classification has no regulatory significance to FDA.

Conclusions

The general policy announced by the federal regulatory agencies is to follow a step-by-step, case-by-case approach to manage the risks of field testing genetically engineered organisms. We regard this policy as prudent, given the lack of knowledge of the effects of these organisms in the environment. As they acquire experience in evaluating such organisms, agencies may be able to develop generic regulations that maintain adequate safety. However, rather than following the policy of developing a more systematic approach based on experience with environmental releases of genetically engineered organisms, USDA and EPA are

[1] This understanding of pathogenicity leads to an apparent paradox: the intra/intergeneric criterion may actually operate in reverse regarding pathogens. Given that closely related organisms are likely to share common traits, then consider a near-pathogen, related to other outright pathogens, which lacks only the proper form of one gene to be able to function as an outright pathogen. This microbe would be more likely to get the missing gene from a more closely related (intrageneric) species than from a more distant one. This would suggest that closer scrutiny be applied for intrageneric than for intergeneric gene transfers into species related to pathogens.

already exempting certain categories of organisms from regulatory scrutiny.

USDA and EPA have established categories for setting levels of review and, in some cases, exempting certain organisms from regulation on the basis of biological features of the source organisms from which the genetically engineered organisms were made. That is, they consider the type of genetic material transferred, the degree of relatedness, and whether pathogenic organisms are involved rather than the nature or behavior of the organism itself. Significant scientific disagreements exist over using each of the three features as exemption criteria. Therefore, while these features may be reasonable criteria for assigning organisms to different levels of scrutiny, we believe that it would be premature to use them as criteria for exempting organisms from regulation altogether.

In one case, USDA has exempted from review any genetically engineered microorganism that is not a plant pest to which has been added genetic material containing only noncoding regulatory regions of DNA. In doing so, USDA concluded that risk from such products is negligible because such transfers do not lead to production of any new material. This exemption raises risk management questions because (1) it is inconsistent with the case-by-case approach for developing exemption categories and (2) it does not acknowledge the potential risk with these organisms that has been pointed out by scientists outside the agency. According to both microbiologists and ecologists, the addition of noncoding regulatory sequences could cause significant changes in the nature and behavior of the genetically engineered organism, thereby presenting a risk of environmental damage. Risk could be reduced by requiring some level of prerelease review by the agency. Consistent with the policy they have adopted, we believe that the agency should consider generic exemptions for organisms of this type only after the organisms have proven to be safe based on results accumulated from a substantial body of cases.

In addition, USDA, under FPPA, exempts from review genetically engineered organisms derived from organisms not on the agency's list of designated pest species or unclassified organisms. This policy may be adequate to manage risks of genetically engineered organisms currently under development. However, a reexamination of this statutory limitation may be warranted as new types of organisms are developed for environmental release.

Similar exemption criteria are also applied by EPA, which regulates genetically engineered microorganisms under FIFRA and TSCA. Under FIFRA, all pesticidal microorganisms are subject to a review system that assigns organisms to different levels of scrutiny prior to release. To regulate introductions of nonpesticidal, nonagricultural commercial microorganisms, the agency will rely primarily on two sections of TSCA. For those genetically engineered microorganisms judged a priori to be of relatively higher risk, EPA requires full review under premanufacture notice or "significant new use" rule requirements in section 5 of TSCA. Applicable microorganisms that fall into the lower risk category, as determined by the criteria discussed above, are exempt from meaningful prerelease review. In its June 1986 policy statement, EPA indicated that it may require an informational report for such organisms under TSCA section 8(a).

We believe section 8(a) provides EPA insufficient authority to take effective regulatory action in the event that review of an 8(a) report raises concerns about environmental impacts. Section 8(a) does not provide a ready mechanism whereby EPA could delay a release while obtaining additional data for a more extensive evaluation. This could be avoided by subjecting all TSCA microorganisms to section 5 premanufacture notice or "significant new use" regulations that allow the agency to impose controls while data are being developed. A multilevel review system, analogous to that employed under FIFRA, could be established within the section 5 review procedures whereby organisms believed to be of lower risk would be initially subject to less detailed regulatory requirements. This approach would provide the agency with the authority to take effective regulatory action, if necessary, while avoiding excessive regulatory burdens on the researcher.

In another case, EPA's planned regulation of environmental releases may be too stringent for certain genetically engineered organisms. Specifically, EPA believes that organisms derived from pathogens are of relatively higher risk than other combinations. Hence, it has proposed subjecting to more stringent review under both FIFRA and TSCA genetically engineered microorganisms formed by combining genetic material between pathogens and nonpathogens. A range of scientists, however, has criticized a part of the agency's categorization of a pathogen, emphasizing that pathogenicity is a complex property that cannot be transmitted to a nonpathogen by transferring just any genes. This criticism raises the possibility that current EPA policy will subject one type of organism classed as pathogens (nonpathogens receiving genetic material from pathogens) to unnecessarily stringent review. Applying stringent

review to a broad group of microorganisms that may not merit it could divert agency resources from other products that may be of greater risk.

Finally, in the past, small-scale field testing under TSCA did not require agency approval. EPA is proposing a rule change to require that such tests of genetically engineered microorganisms be reviewed by the agency before field release if field testing is conducted with commercial sponsorship. If they are performed by academic researchers at an institution receiving any federal funds, these same field tests would not be subject to TSCA but would come under the jurisdiction of the NIH-RAC or the USDA Agricultural Biotechnology rDNA Advisory Committee. However, the same experiments by academic researchers at an institution independent of federal funds, if performed for noncommercial purposes, could result in releases that go unreviewed. At present, the need for remedial action to close this gap in coverage is uncertain because the number of applicable experiments appears to be small.

Recommendations

To ensure that microorganisms formed by the transfer of "well-characterized noncoding regulatory sequences" of genetic material from plant pests to nonplant pests receive review prior to release, we recommend that the Secretary of Agriculture direct the Administrator, APHIS, to revoke the exemption for such organisms in regulations governing genetically engineered plant pests.

To ensure effective regulatory coverage of genetically engineered microorganisms, we recommend that the Administrator, EPA, make all microorganisms covered by the Toxic Substances Control Act subject to either the premanufacture notice or "significant new use" rule regulations prescribed by section 5 of the act. To avoid overregulation of lower risk organisms that could result from this action, EPA could revise section 5 regulations to establish a multilevel review system with less stringent requirements for organisms believed to be of relatively lower risk.

Agency Comments and Our Responses

Department of Agriculture

USDA commented that our recommendation to revoke the exemption for microorganisms formed by transferring well-characterized noncoding

regulatory regions from plant pests to nonplant pests is unnecessary. The agency stated that its position is based on the limited nature of the exemption and its review of scientific opinion and scientific literature. Furthermore, it stated that we did not fully consider the comments of the scientific societies critical of its exemption policy. USDA asserts that its final rule conforms to the recommendation of some critics to narrow the exemption.

We find no evidence of a narrowing of the exemption in USDA's final rule. A comparison of the definition of "regulated article" in section 340.1 of USDA's final rule with that in the proposed rule shows that the scope of the exemption remained unchanged. Moreover, the central concern of scientific societies in question was that the addition of noncoding regulatory sequences may substantially change the biology of the recombinant microorganism and could cause problems in some circumstances. This concern is not fully acknowledged in USDA's discussion of the exclusion in the preamble to the final rule.

We continue to believe that the exemption is premature. The basis for our recommendation is that microorganisms modified by the insertion of well-characterized noncoding regulatory sequences may be sufficiently altered to deserve regulatory scrutiny before release into the environment. There is no dispute with the USDA position that transfers of genetic sequences are incapable of producing any new kind of gene product. However, this kind of engineering can change the amounts of gene products affected by the regulatory sequences. Altering the amounts of gene products could cause significant changes in the functioning of the microorganisms. In this regard, very little empirical evidence is available to predict the behavior of microorganisms that have received regulatory sequences from other organisms. A professor of microbiology, who has testified on behalf of the American Society for Microbiology at congressional hearings, went as far as characterizing the USDA exemption as being "scientifically indefensible."

A further justification for our recommendation is the soundness of the USDA's underlying regulatory policy. In an area where the agency lacks experience and knowledge, a cautious approach would not exempt categories of genetically engineered organisms from review until their safe use in the environment has been adequately demonstrated. We believe that USDA's regulatory procedures are sufficiently flexible to accommodate such information as it becomes available. Until that time, however, the lack of evidence to support the exemption is grounds for recommending its revocation.

Environmental Protection Agency

EPA noted its awareness of the issues raised in the report concerning the types of microorganisms that should be regulated. The agency pointed out that its approach to regulating biotechnology products has been subject to change since the publication of its 1986 policy statement and is still under development. EPA stated that the concerns that we identified are being evaluated and will be addressed in its proposed rules. (These are expected to be issued in June 1988.)

To better reflect the evolving nature of EPA policy, we have added to this chapter a description of a regulatory option currently under consideration by the agency, the establishment of Environmental Biosafety Committees.

Health and Human Services

HHS' comments were critical of our discussion of regulatory policies and our recommendations to USDA and EPA. Among HHS' concerns is the need to evaluate all proposals involving releases into the environment. The agency stated that the case-by-case review policy endorsed by the OECD, NAS, and others differs from our understanding of the concept. To HHS, case-by-case means that each case that warrants review should be assessed against criteria tailored to that particular proposal; it does not mean that every case requires regulatory scrutiny.

Earlier in this chapter, we discussed the rationale and precedent for setting up a regulatory framework that starts with comprehensive coverage and moves toward selective coverage as knowledge and experience are gained over time. Whereas HHS believes that categories of products may already be defined that do not require regulatory oversight, we believe that sufficient scientific data are not yet available to justify exemptions from review. This view, the premise for our recommendations, was supported in a 1988 study by the Office of Technology Assessment that concluded

> "In sum, although the characteristics of engineered organisms make certain kinds less likely than others to cause problems, it is not now possible to describe any broad categories that could be completely exempted from review. Counterexamples can be provided from existing experience to negate almost any proposed category for exemption from review."

HHS' comments and our responses are discussed in detail in appendix VI.

Administrative Mechanisms for Risk Management

Decisionmakers seek to balance the insufficiency of relevant data on risks of releasing genetically engineered organisms into the environment against the need to make timely regulatory decisions to promote industrial development and commercialization of important new products. They must also strike a balance between imposing control mechanisms to guard against potentially dangerous consequences and allowing the test to generate data reflecting realistic conditions. This chapter examines how USDA, EPA, and FDA implement their regulatory policies and procedures for risk management.

The agencies' administrative approaches are discussed in terms of the data requirements and scientific reviews in the prerelease evaluation process, decision criteria, and conditions required for the control and management of field testing. Individual cases already evaluated by the agencies are cited to show how the review process has been applied to the first applications that they have received.

Agencies appear to be moving cautiously with regard to genetically engineered organisms, evaluating each product on a case-by-case basis. They have established an essentially ad hoc regulatory approach, directed at assembling the available data for a particular product and applying the judgment of a group of qualified scientists to determine whether the proposal should be approved and under what control constraints.

Specific information on risks, design of the field trial, monitoring procedures, and mitigation methods is generally included in the overall testing plan and supporting data submitted by the applicant. Before a release is approved, scientific advisory groups evaluate the application and determine the data needed to demonstrate product safety. A risk-benefit analysis may also be required before a final decision is made. The decision by an agency to approve a field test usually binds the researcher to conduct the test according to the conditions stated in the application. A preventive approach, entailing careful prerelease screening, is the most effective risk management for field trials.

Data Requirements and Scientific Reviews

As noted in chapter 2, the Coordinated Framework indicates a consensus that agencies should (1) use scientific reviews of comparable rigor and (2) include scientists from each other's staffs in product evaluations. Procedures are being established at several agencies to implement this policy. A description of the data requirements and review mechanisms of each regulatory agency follows.

Department of Agriculture

USDA regulates the environmental use of genetically engineered organisms in two primary areas: veterinary biological products and plant pests. To assess the potential risks of veterinary biological products containing live, genetically engineered organisms, APHIS requires data derived from testing under contained conditions. The data should describe the parental organism, the effect on it of the gene alteration (focusing on survival, reproduction, and dispersal), and information about genetics and ecology of both parental and modified organisms.

APHIS' veterinary biologics staff analyzes all field-test proposals. The disciplines represented by its staff members include microbiology, veterinary medicine, population genetics, immunology, and public health. Their finding is then reviewed by the Veterinary Services Biotechnology Committee. This is a standing, interagency group composed of representatives from APHIS' National Veterinary Services Laboratories, the Food Safety and Inspection Service, the USDA Office of General Counsel, and the FDA.

In determining whether to issue a permit allowing the release of a plant pest that is genetically engineered by rDNA techniques, APHIS evaluates the pest risk by reviewing the scientific literature and by examining data developed from research within a contained facility. An application must include information on the anticipated or actual expression of the genetic material in the regulated article (defined in ch. 2) and its characteristics, the molecular biology used to produce the product, the country of origin of the source organisms, the proposed experimental design, and related information.

Critics from environmental groups contend that USDA reviews under FPPA are inadequate to address issues of ecological safety. By focusing the evaluation on the genetically engineered organism's plant pest risk, they assert, USDA is not requesting sufficient information from the applicant to assess an organism's behavior in the environment and its potential ecological risk.

APHIS officials dispute this criticism, pointing out that an examination of environmental effects is required, under the National Environmental Policy Act, when the agency takes action on each individual application. Prior to issuing a permit for the release into the environment of a genetically engineered organism, APHIS must prepare an environmental assessment or, where there may be significant environmental consequences, an

environmental impact statement. Information used in preparing its evaluation comes from data submitted by the applicant, a search of the relevant scientific literature, and information received through coordination with other regulatory agencies.

APHIS' biological assessment support staff within the Plant Protection and Quarantine (PPQ) Division is responsible for issuing permits for the introduction of a genetically engineered organism. It has up to 120 days to review a completed application. The staff has expertise in plant pathology, entomology, botany, virology, and other scientific disciplines. For each permit request, a pest risk assessment is conducted by a staff specialist in consultation with other specialists at USDA, universities, and industry. To determine the adequacy of the test site, APHIS may conduct a site inspection prior to issuing a permit.

Before issuing a permit for an environmental release, APHIS must coordinate and consult with the state where the release is planned. It must submit a copy of the application to the state department of agriculture for notification and review. State regulatory officials are expected to provide specific environmental and ecological data on the test site and to assist in the enforcement of the federal regulations.

PPQ has reviewed a number of applications under FPPA. Prior to the issuance of the final rule in July 1987, the submissions included an application to field-test herbicide-resistant tobacco developed by Ciba-Geigy Corporation, a request from Rohm and Haas Company to field-test a genetically altered insect-resistant tobacco plant, and a proposal by Monsanto Corporation, subject to joint review with EPA, to test genetically engineered bacteria as microbial pest control agents. In the Monsanto case, APHIS asked for additional tests to determine host range (the span of organisms in which a parasite can reproduce) before a determination of plant pest status could be made. In the other cases, APHIS issued opinion letters stating that the genetically altered tobacco plants did not present a plant pest risk Between July 1987 and February 1988, APHIS issued five permits for introductions of genetically engineered plants after preparing an environmental assessment on each proposal.

All evaluations relating to animals or plants are prepared by APHIS program staff and examined by APHIS' Biotechnology Environment Coordination Staff. Depending on the type of organism, the novelty of the experiment, or a particular scientific issue, the field-test proposal may be referred to a genetic engineering oversight panel. USDA has established an Agriculture Biotechnology Research Advisory Committee,

modeled after the NIH-RAC to review research proposals and to provide scientific advice to research and regulatory agencies. The committee consists of nine nongovernment reviewers with a broad range of expertise, including genetic engineering, ecology, agricultural production, regulation, and public health. In addition, four federal agencies provide technical support.

Environmental Protection Agency

In its policy statement on regulating microbial products, EPA stated that specific information needs will be determined on a case-by-case basis, and non-agency experts with specific knowledge of the relevant microorganisms will frequently be used to assist in reviews. Genetically engineered microorganisms in the categories judged to pose relatively high risk will receive full scrutiny before an environmental release, even at a small scale. The extent of prerelease review, if any, for TSCA microorganisms judged to pose lower risk will be announced in future rulemaking. In general, EPA scientists conduct the scientific review and risk assessment. If appropriate, other federal agencies and independent expert consultants provide review and comment.

EPA has established a Biotechnology Science Advisory Committee (BSAC) to provide peer reviews of specific product submissions under FIFRA and TSCA. The committee consists of independent scientists, members of the lay public, and nonvoting representatives from other federal agencies involved in regulating genetically engineered organisms. The scientific members of the committee provide a range of expertise for assessing scientific and technical issues, such as questions of hazard, exposure, and risk to humans and the environment. Separate, specialized subcommittees may be formed when necessary. The following two sections describe the information sought and the review process used in conducting product evaluations at EPA.

FIFRA

In regulating microbial pesticides under FIFRA, the agency has adopted a two-level review system. As discussed in chapter 2, genetically engineered microorganisms formed from nonpathogenic sources that are not intergeneric combinations are considered less likely to pose significant risks. For small-scale field testing (involving 10 acres or less), microorganisms of this type are subject to less detailed level I reporting requirements and abbreviated review prior to release. Level I reports should summarize the microorganism's (or its parental strain's) identity, natural habitat, host range, relative environmental competitiveness (if available), and genetic and behavioral features and should describe the

proposed testing program. Producers are to be notified within 30 days whether the field testing may proceed. Should EPA's preliminary assessment raise concerns indicating that additional information or monitoring is needed, the applicant must either apply for an environmental use permit (EUP) or submit additional data for a full notification (giving the agency 60 additional days for review).

Level II full notification is required for small-scale field testing of microorganisms believed to pose a greater probability of harm. These include genetically engineered microbial pesticides formed by intergeneric combinations or derived from pathogenic source organisms. Full notification requires the submission of background information on the microorganism (the same data elements required under level I but with greater specificity) and a detailed description of the proposed field test. EPA has 90 days to review each notification to determine whether an EUP is required.

Scientific reviews are conducted by the Office of Pesticide Programs (OPP) to assess the potential risks associated with each proposed experiment. OPP prepares a formal paper identifying potential problems or unanswered questions and a statement of the overall likelihood of significant risk. The staff represents a range of expertise. For the review of Advanced Genetic Sciences' (AGS) proposal to test ice-minus bacteria on strawberry plants, for example, the hazard evaluation review team had expertise in biology, microbiology, and plant pathology.

If the proposed field test raises complex or controversial questions, the notification data would also be submitted to a group of independent scientists constituting a subcommittee of the BSAC. In the case of the AGS application, for example, OPP's preliminary assessment was reviewed by such an ad hoc advisory subpanel (then part of the FIFRA Scientific Advisory Panel) as well as EPA's Intra-agency Work Group on Biotechnology, USDA, NIH, and FDA.

TSCA

Under proposed TSCA rules, all field testing of genetically engineered microorganisms formed either by intergeneric combinations or from pathogenic source organisms will be subject to full notification and review, while releases of other genetically engineered microorganisms may require, at most, submission of an abbreviated report. Agency risk assessments require data on exposure, environmental fate, and human

health and environmental effect · Manufacturers are expected to provide test data demonstrating the microorganism's safety, including general background information on the source organism, as well as data indicating the microorganism's potential for survival, replication, dissemination, and genetic transfer.

In a full review, EPA's Office of Toxic Substances (OTS) will have 90 days (with a possible 90-day extension) after filing a premanufacture notice to decide whether to prohibit or limit field testing. In its risk assessment, OTS integrates hazard and exposure assessments on the basis of the information submitted. It also identifies major areas of uncertainty, if any, and areas where additional data are needed. Before making a regulatory recommendation, OTS evaluators may consult with external scientific experts, and their analyses may be reviewed by peers on a subcommittee of the BSAC.

EPA's first premanufacture notice for a genetically engineered microorganism under TSCA was a submission by BioTechnica International (BTI) to test the ability of bacteria engineered for enhanced nitrogen fixation to promote yield increase in alfalfa. A panel composed of highly specialized representatives from EPA, USDA's Agricultural Research Service, university plant science departments, and state government was formed to discuss issues raised in the risk assessment. In the draft consent order stipulating conditions under which the BTI field study could proceed, EPA noted that

"During the process of evaluating the [premanufacture notice] microorganisms, the Agency examined every issue considered to be clearly or remotely relevant, even if the issue were hypothetical. For this particular review, the Agency is exceeding what it expects to commit in time and resources to future reviews of similar organisms, once the review of genetically engineered microorganisms becomes more commonplace. With experience gained in reviewing a number of genetically engineered microorganisms, the Agency expects to be able to reduce the number of issues examined in detail in each review, to isolate and concentrate on the few relevant issues, and to reduce the Agency resources committed to each review."

For other genetically engineered microorganisms subject to TSCA,[1] EPA may propose a reporting rule for gathering general information prior to introductions into the environment. Although it has not yet specified all the required information, the agency may collect data "to fulfill its responsibility to identify and prevent important or immediate hazards

[1]These include nonpathogenic intrageneric organisms as well as intrageneric organisms derived from opportunistic pathogens or from organisms involved in mutualistic interactions or certain other types of biological relationships. (See ch. 2.)

that might unexpectedly arise" from environmental releases. EPA has indicated that it will consider the availability of information and the economic impact on the manufacturer in developing data. As explained by an agency reviewer, EPA sees a tradeoff between the greater certainty about the safety of an environmental release based on more prerelease testing and the amount the investigator can spend to develop a product.

Food and Drug Administration

In its final policy statement in the Coordinated Framework, FDA indicated that the agency will apply to genetically engineered live viral vaccines its past approach to reviewing nonengineered human vaccines. While the burden of proof of the product's safety and effectiveness is placed on the manufacturer, agency scientists conduct reviews to appraise the risks involved with each product on the basis of its intended use.

The scope of information required to be submitted will be determined separately for each case. In general, however, an investigational new drug (IND) application must contain information to demonstrate the safety of proceeding to test the product on human subjects. This includes product composition, methods used in production, results of animal research, training and experience of investigators, and a plan for clinical investigation. Once a complete data file has been submitted, FDA has 30 days to decide whether to request that the sponsor of the proposed clinical study continue to withhold or to restrict use of the product on human subjects.

Data submitted in support of an IND are evaluated by the Center for Drugs and Biologics' Office of Biologics Research and Review. The notice is circulated for review to staff research scientists selected for their specific area of expertise. In the case of an IND application for a new, genetically engineered vaccine, scientists in the Division of Virology and the Division of Biochemistry and Biophysics would be used in deciding whether it is safe to initiate clinical testing.

Although FDA does not foresee a special advisory committee for genetic engineering, it can obtain outside scientific expertise through its existing committees organized according to product categories. For example, a live viral vaccine proposal could be sent for review to the Vaccines and Related Biological Products Advisory Committee, which is composed of specialists from hospitals and medical schools. Such consultation has taken place only rarely in the past, but when the subject is controversial

and the agency wants "externalization of judgment" on the reasonableness of its approach. FDA may send a vaccine proposal to the advisory committee.

Field Testing Approval Criteria in Agency Decision-Making

One of the three basic approaches to risk management discussed in chapter 1 involves the balancing of risk against other factors such as benefits, costs, alternatives, and even other risks. Although EPA is required by law to conduct formal risk-balancing analyses, FDA and USDA do not have such explicit requirements. This section discusses the use of risk balancing and the extent to which secondary effects are considered in agency decision-making.

Agency decisionmakers have applied the risk-balancing approach to a limited extent with regard to small-scale field testing. In general, federal regulators have given more attention to risks than benefits in this field-testing stage. APHIS officials see their mission as the prevention and eradication of agricultural problems. EPA's use of risk-benefit analyses for field tests has focused more heavily, but not exclusively, on minimizing health and environmental risks. Traditionally, FDA's approach has been to consider only health-related risks and benefits.

In addition to direct impact on health or the environment, consideration of potential secondary effects may enter into the risk-balancing process. According to critics of biotechnology, products must be examined within the total context of their expected use. They urge that evaluations be conducted not only for a product's direct effect on the environment but also for its long-term economic and social consequences. Among the early concerns to emerge as a result of genetic engineering applications have been the potential for significant changes in the use of agricultural chemicals and the structure of the agricultural economy.

Developing plant varieties genetically engineered to resist specific herbicides could have significant effects on weed control practices. While they may offer the potential for short-term gains in agricultural productivity, they have raised environmental concerns. It has been argued that herbicide-resistant crop plants will intensify the use of chemical herbicides. An agriculture specialist of a national environmental group has argued that it "will extend the pesticide era rather than end it, continuing the health and environmental risks associated with pesticide use."

Another broader agricultural issue that may require analysis is farm productivity and profitability. An independent advisory group has recommended that USDA conduct economic reviews early in the development of the new technology to determine the impact on farm labor, subsidy programs, and world competitiveness. In a report to the President and the Congress, the National Agricultural Research and Extension Users Advisory Board criticized USDA for not conducting necessary benefits analyses.[2] It stated that

"An inexpensive technology can be a useful strategy for increasing profitability and reducing the need for subsidies. . . . On the other hand, if a relatively high-cost technology significantly increases production in a glutted market, the market price can fall sufficiently to erase any increase in profitability which the farmer may temporarily receive from adopting the technology. In a subsidized market, the American taxpayer pays a share of the bill for the new technology."

Public decisionmakers may be reluctant to consider the broader implications of developing this technology due, in part, to regulatory constraints. Given that the legislative mandates under which the agencies operate do not require such analyses, regulators may be unwilling or unable to address these concerns in the review process because they believe they lack sufficent authority to do so.

Department of Agriculture

USDA's regulatory goal is the exclusion and eradication of plant and animal pests. In general, permitting of plant pests or authorization of animal biologics for field testing is premised on the avoidance of risk and does not involve a formal assessment of risks and benefits. The agency adheres to a "de minimis" approach, in which the risk is held as close to zero as possible. Although the broader economic impact is not analyzed, APHIS may identify benefits expected to result from commercial-scale use of the product to be tested.

This approach was evident in the agency's review of a proposal by the Upjohn Company and the Diamond Scientific Company to test a new veterinary biologic, a genetically engineered swine pseudorabies vaccine. The approval decision was based on a finding of no significant environmental risk associated with the field test. The benefits of the field test were viewed in terms of the potential gain to farmers of commercializing the product. In the document authorizing the field tests,

[2]National Agricultural Research and Extension Users Advisory Board, Appraisal of the Proposed 1988 Budget for Food and Agricultural Sciences (Feb. 20, 1987).

APHIS noted that a decision to refuse shipment would prevent the manufacturer from developing the data required for licensing. This would, it further noted, prevent the licensing of the vaccine and prohibit its sale in the marketplace, thereby denying farmers a possible solution to the problem of controlling pseudorabies.

Another example is APHIS' review of a field-test proposal submitted by Ciba-Geigy Corporation for a genetically engineered tobacco plant altered to make it resistant to the herbicide atrazine. The objective of the field test, according to the applicant, was to determine whether environmental factors that could not be duplicated in the laboratory or greenhouse would influence important characteristics of the new plant. APHIS' evaluation found that the field test would not present a substantive plant pest risk or have a significant impact on the environment. Neither small-scale benefits nor commercial-scale risk and benefits were acknowledged in the agency opinion letter.

Environmental Protection Agency

EPA described its criteria for regulatory decisions in its Coordinated Framework policy statement. In regulating genetically engineered products, the agency is required under both FIFRA and TSCA to consider the potential benefits to society along with potential risks. While the risk assessments are developed by OPP or OTS staff, agency economists estimate the benefits of the product on the basis of information from the submitter, independent economic research, and consultation with nonagency experts.

The agency has made limited use of risk-balancing analysis in its decisions on field testing genetically engineered organisms. In judging whether a risk is unreasonable, the analysis appears to focus more on risks than benefits, at least in the small-scale testing stage. Hazard and exposure assessments are conducted to determine the potential effects on humans or the environment from the specific proposed release. On the benefit side, the agency and the company expect small-scale testing to provide valuable scientific data on the nature and behavior of the organisms in the environment and on the efficacy of the product. They acknowledge that commercial-scale use of the product may offer broader economic or environmental advantages.

The agency recognizes that both the risks and benefits may increase with commercial scale-up. In the case of the AGS proposal to test a genetically engineered organism that might protect strawberries against frost damage, the potential benefits included the economic gain from

crop protection and the development of an alternative to certain persistent, toxic chemicals currently in use. Critics of the proposal expressed concern that widespread use of the product could be disruptive because it might alter rainfall patterns.[3] Although EPA required modifications in the design of the test for better monitoring of the organism's dissemination into the atmosphere, it acknowledged that a small-scale field test would not be sufficient to provide definitive information on this potential risk.

Another example is the agency's decision regarding the BTI proposal to field-test organisms genetically engineered to enhance nitrogen fixation so as to improve legume crop yields. The EPA draft consent order reflected a cautious risk-balancing approach. The direct benefit expected by the agency was the development of data on efficacy and environmental effects. Broader benefits anticipated from commercial-scale use of the product included lowering farm production costs, freeing land for other uses, and reducing the use of fertilizer. The agency decided that the experiment would not present an unreasonable risk to health or the environment if the company conducted the field test under prescribed conditions. However, the genetically engineered organisms were not to be added to the TSCA chemical substance inventory until activities beyond research and development began. This is not expected until well after the 3-year field test (during which time EPA may decide to require a "significant new use" rule). These measures were intended to prevent uncontrolled testing or larger scale releases without further evaluation of the potential effects of expanded uses in the environment.

Food and Drug Administration

FDA statutes neither require risk balancing nor specify risk standards. However, under the agency's long-standing case-by-case evaluation procedures, the benefits of a new product are considered along with the risk of public exposure to a potential health hazard. According to one agency official, decision-making is based, to a considerable extent, on "common sense medicine" in which the level of acceptable risk may fluctuate in response to additional factors. Defining an acceptable risk-benefit quotient depends on certain considerations, including the purpose of the product, the target population, the characteristics of the organism, the seriousness of the disease, and availability of alternative treatment.

[3]Scientists advocating the release of "ice-minus" bacteria responded to this concern by pointing to experimental proof that the modified organisms would not colonize plants beyond those onto which they were initially placed. They also noted that, even if used commercially, the altered bacteria would only be used on low-acreage specialty crops. They concluded, therefore, that the use of ice minus would not substantially change the amount of nuclei provided to the atmosphere for rain formation.

The FDA official stated that, in deciding whether to allow the use of a new drug or vaccine in early clinical trials, regulations place more emphasis on safety than on efficacy. At the same time, a reviewing scientist with the agency pointed out, the benefits to the individual must at least match its risks, otherwise the IND application will be rejected. In a case where a vaccine is proposed for testing on healthy infants, the level of risk would have to be very low to be acceptable. On the other hand, in cases involving experimental treatments for life-threatening diseases, the level of acceptable risk may be higher. For example, in testing a live, rDNA vaccine for AIDS, FDA might accept a higher level of risk, perhaps in the form of significant side effects, in the hope that the vaccine would prove helpful or provide valuable data.

Conditions for Field Testing

Given the understanding that zero risk is not possible, control and management measures are also considered in regulating environmental releases. Scientists generally agree that efforts to control the dispersion and impact of genetically engineered organisms should correspond to the degree of risk associated with the specific release. Designing field trials to mitigate risk was an issue discussed at the Shackelton Point Workshop on Biotechnology Impact Assessment, held in October 1985.[1] Reports by working groups, each consisting of experts from industry, regulatory agencies, universities, and public interest groups, were prepared as a risk management guide to policymakers and regulators.

According to these experts, the overall test plan approved by an agency should include information on the characteristics of the test site (for example, location, composition, whether it borders land or water) and method used to apply the organisms. Because of the potential for inadvertent dispersal by attending staff or equipment, precautions for workers and materials exiting the site were considered appropriate. In addition, the problem of dispersal by unauthorized intervention could require limiting physical access or other forms of security to control and manage the test effectively.

In order to assess the success of containment, researchers should monitor field-test sites for the survival and dispersal of the introduced organism. Among the considerations to be included in a monitoring plan are

[1]Prospects for Physical and Biological Containment of Genetically Engineered Organisms: The Shackelton Point Workshop on Biotechnology Impact Assessment, October 1-4, 1985, ed. James W. Gillett, Ecosystems Research Center Report No. ERC-114 (Cornell University, March 1987).

the method, location, and frequency of sampling. If containment methods fail, the investigator should be prepared to implement mitigation measures to limit spread beyond the field plot. Contingency planning prior to field testing should ensure reliable means of correcting any problems arising from an inadvertent failure of controls. Mitigation plans should identify biological and physical methods available to reduce or eliminate the introduced organism. For a description of technical methods for risk management and mitigation, see appendix I.

Department of Agriculture

USDA officials have emphasized their extensive experience in the use of preventive and remedial measures to protect agricultural animals, crops, and forests. Reviews of tests of genetically engineered organisms would be managed in a way similar to the agency's handling of imported organisms with regard to their possible impacts on agriculture under VSTA, FPPA, and PQA. Persons receiving approval are required to agree to abide by all the conditions imposed by USDA regarding testing, use, and disposal of the experimental product. If a violation of the regulations occurs, the person is subject to administrative, civil, or criminal penalties as provided under these acts.

To authorize shipment of an unlicensed animal vaccine for research purposes, APHIS must determine that the conditions under which the experiment is to be conducted are adequate to prevent the spread of disease and then approve the procedures set forth in the request. Such testing may involve special restrictions, as set forth in the environmental assessment prepared by Veterinary Services. If, despite control measures, a released genetically engineered organism is found to cause disease in animals, APHIS has the authority to implement immediately an eradication program under the Regional Emergency Animal Disease Eradication Organization.

An example of the APHIS approach to stipulating testing procedures for a veterinary biologic is the case of the Upjohn/Diamond Scientific recombinant-derived, live pseudorabies viral vaccine for use in swine. In authorizing the proposed field safety-efficacy studies, the agency required the test farms to be under strict quarantine conditions, thereby restricting their contact with other hog-producing farms. In addition to monitoring all test animals for any adverse reactions, the researchers were to observe all non-test animals for possible spread of the vaccine virus on the farm. If trial animals became infected with the pseudorabies virus, they were to be disposed of, while other trial animals would

eventually be marketed. At the end, a summary of the results had to be reported to APHIS.

For field-testing plants, an application to introduce a genetically engineered organism with rDNA must include a detailed description of the safeguards to prevent its escape from the test site. In cases where APHIS issues an opinion letter stating that the product was found not to be a plant pest, then the particular test, when carried out implementing the containment and mitigation measures stated in the application, is not subject to further requirements.

If, after review by PPQ, APHIS grants a permit, it will specify standard and supplemental conditions for the release. Standard conditions include general stipulations concerning procedures for maintenance and disposal of regulated articles; remedial measures to prevent the spread of plant pests; monitoring reports by the permittee on the performance of the regulated article; and, in the event of an accidental release or unexpected development, notification of PPQ within a specified time.

In the event of an accidental escape of a plant pest, APHIS has available emergency procedures. Statutory provisions authorize USDA to quarantine an area if necessary to prevent the spread of a dangerous plant disease or to take other remedial measures to dispose of any product capable of causing damage to agriculture. Additionally, if it finds that an article that is prohibited or restricted by regulation is being introduced, USDA is authorized to seize and dispose of it.

Environmental Protection Agency

Standard criteria for siting, containment, monitoring, and mitigation have not been developed by EPA. Rather, it is the responsibility of the applicant to devise risk management procedures most appropriate for its particular field studies. However, EPA requires and evaluates data on the design of the testing program in the process of conducting its risk assessment. Agency approval of the release of genetically engineered microorganisms is contingent on the applicant's implementing measures specified in the notification or modified or added by the agency.

The submitter is expected to provide information describing the location of the site relative to human populations, as well as its geographic, physical, chemical, and biological features. An outline of containment measures should indicate the procedures to protect the test area from intruders and the method of disposal or sanitation of exposed plants, animals, soil, and other materials. To monitor the microorganisms within

and adjacent to the site, the applicant should identify detection and sampling procedures. Investigators should describe methods available for terminating the test and reducing dispersal beyond the site in the event of an accidental release.

The agency's approval of AGS' proposal to field-test ice-minus bacteria illustrates how it considers these risk management factors in the review process. EPA first awarded a permit to AGS in November 1985. However, in early 1986, the agency learned that the company had injected the frost-resistant bacteria into trees on the roof of a building before receiving agency approval. EPA subsequently withdrew the permit, conducted a check of the company's records, and fined the company $13,000 for violating FIFRA. The agency reinstated the AGS permit for a new test site in February 1987.

EPA, along with California state officials, inspected three alternative test sites. The agency's evaluation of the sites was based on two criteria: (1) the presence of any site characteristics that would lead to significant risks and (2) the ability to conduct the associated monitoring and contingency measures as proposed. (EPA indicated that its preference to have the testing done in an isolated or remote area with restricted access was relevant primarily to public acceptance.) Applicators were instructed to wear full protective clothing to minimize exposure to the aerosolized microorganisms. EPA examined the specific design for sampling (including the location, frequency, and methods) of the treated plants, insects in the test plot, soil, and neighboring untreated plants. If the bacteria were detected beyond the test site, provisions in the permit called for spraying a biocide to control the organism. Reports on the data obtained from the experiment were required to be submitted every 90 days.

Food and Drug Administration

FDA officials are confident that the agency's extensive experience in regulating new biologics is applicable to products containing genetically engineered organisms. They discussed genetically engineered vaccines made by adding genes from disease organisms to the virus "vaccinia." They pointed out that two centuries of experience with vaccinia as a smallpox vaccine have provided considerable clinical knowledge about products derived from this virus. This, in combination with laboratory knowledge of genetic engineering techniques used to manufacture new human viral vaccines, serves as a basis for overseeing the clinical testing.

A live viral vaccine is biologically active and is intended to replicate in the recipient. The virus may be transmitted from the vaccinated person to others through a process called "shedding." Shedding is not necessarily undesirable because it may lead to immunization of others in the population. (It would, however, be undesirable if the secondary infections produce disease.) This potential for shedding is not known, and its determination is one of the objectives of testing. For FDA risk managers, the degree of concern about transmission dictates the level of containment that FDA would require for clinical investigations.

In general, FDA has no standard controls for limiting the risk of transmission for studies involving live viral vaccines. Specific precautions by the investigator are outlined in the IND submission, and their adequacy is determined by FDA on a case-by-case basis. The agency relies on good medical practices by those conducting the trials for the protection of health workers and other personnel. Containment is achieved through safety practices such as decontamination, waste disposal, and emergency procedures. It may also include physical isolation. In the case of an AIDS vaccine, early clinical testing would be done in a hospital ward under the same conditions as a typical infectious disease ward.

Responsibility for monitoring the testing for compliance with the conditions set up in the IND rests with the study's sponsor. If a company is suspected of violating agreed-upon protocols, FDA's Division of Scientific Investigations can examine how the clinical work is being carried out.

Summary

USDA, EPA, and FDA have established procedures implementing their policies for prerelease reviews of proposals involving genetically engineered organisms. The agencies have identified general data requirements and possess the authority to request additional data as needed to evaluate individual proposals. Their scientific advisory groups reflect a wide range of relevant disciplines. USDA and EPA may combine the expertise of various federal agencies in their product reviews and coordinate with state regulatory officials.

The agencies have tended to emphasize risk reduction in their reviews of the first cases involving the release of genetically engineered organisms in the environment. They have carefully scrutinized the potential risks of several proposed field releases and have given limited attention to the potential benefits. The chief benefit of field testing is the development of information needed for subsequent regulatory decision-making on the proposed or other similar products. In deciding on these first field tests,

the agencies have generally not taken into account the possibility of secondary risks, especially in the area of social and economic impacts on agriculture and the use of agricultural chemicals. Critics are urging that greater attention be given to this broader range of risks. Others have questioned whether analyses of such issues are an appropriate part of the regulatory process.

Conditions for field testing stress the importance of designing tests to control and monitor the migration of genetically engineered organisms from the site of release. The agencies can apply special conditions as needed to manage the risks associated with the movement or release of such organisms. They also generally require plans for mitigating any unexpected harm that might occur and possess the authority to limit or terminate an experiment, if necessary.

Technical Methods for Risk Management

While chapter 3 examined the regulatory activities of the relevant agencies, this appendix describes the technical methods available and under consideration for managing the risks of intentional releases of genetically engineered organisms into the environment. It discusses methods for controlling the organisms and preventing transfer of their acquired genes to other organisms, for monitoring the organisms and the genes during field tests, and for mitigation to be used to end a test early or to eliminate remaining organisms after a test in order to prevent undesired impacts.

The survey of technical control, monitoring, and mitigation methods that follows is largely based on the proceedings of the Shackelton Point Workshop (SPW) held by the Cornell University Institute for Comparative and Environmental Toxicology.[1] The workshop was composed of a broad range of academic, industrial, regulatory agency, and public interest group experts on biotechnology.

The SPW concluded that efforts to limit the dispersion and impact of genetically engineered organisms should begin by establishing appropriate criteria for containment, monitoring, and mitigation. The need for containment is determined by the degree of risk associated with a potential failure of containment. In some instances, it may be that a genetically engineered organism poses such an acceptably low risk that exposure management may not be necessary. In other cases, no control methods may be adequate to limit dispersal from the test site. If difficulties in containment are too great when compared with potential risks, then it may not be safe to release the organism, and the field test should be disallowed.

Based on the criteria developed from the specific risk assessment, combinations of physical and biological techniques can be applied to control the survival, growth, and dissemination of the engineered organism and its DNA. However, using containment methods often compromises field-test results by imposing artificial interactions or precluding natural processes. Physical and biological controls reduce the realism of the test and add to the uncertainty about the efficacy and impacts of releasing genetically engineered organisms into the environment.

[1] "Prospects for Physical and Biological Containment of Genetically Engineered Organisms: The Shackelton Point Workshop on Biotechnology Impact Assessment, October 1-4, 1985."

Few products can be tested in the environment and be truly contained. For plants, which present the fewest management difficulties, techniques for controlling the spread of engineered plant genes include containing pollen escape and preventing seed development or release. For genetically engineered microorganisms, no single method of containment is absolute. Therefore, several methods should be used to restrict dispersal via insects, air circulation, water runoff, and other modes.

The SPW participants agreed that valid monitoring and mitigation methods are a prerequisite to field testing. Most monitoring techniques used to track the movement of the organism have serious drawbacks in either sensitivity or specificity. Therefore, if possible, a monitoring plan should also include effects monitoring to detect the impacts caused by the organisms in the environment.

Because risk management approaches often differ widely between types of organisms, technical methods for bacteria, viruses, and plants are presented separately below.

Controlling Survival, Multiplication, and Spread

Considering the reasons for genetic engineering of organisms, ecologists point out that often the objective is to produce an organism that can overcome some biological limit that constrains the parent organism. Examples include enabling an organism to live on a wider range of food sources or to tolerate more extreme temperatures, moisture, or other chemical conditions; or, for a parasite, to live off a wider range of hosts. Any of these actions can make it possible for the engineered organism to expand substantially beyond the range of its parent species. Furthermore, the method of releasing a genetically engineered organism is generally chosen to give it a high probability of surviving, at least until its intended mission is fulfilled. Taken together, these practices can increase the probability for the organism's survival, multiplication, and spread. For purposes of risk management, the organism should be designed in a way that limits the expansion of its range. If this is not possible, at least those working with the organism should be prepared to otherwise control or prevent the engineered organism from escaping beyond its intended range.

Physical and biological methods can be adopted to control the survival, multiplication, and spread of genetically engineered organisms in a field test. Physical control means restraining or limiting the organism through manipulating its environment by using mechanical, physical, or nonspecific chemical barriers. An example would be screening over a test site

to prevent access by insects and birds that could carry experimental microorganisms away with them. A biologically controlled organism is one that has a trait that can be exploited or manipulated to limit or control the organism in particular environments. An example would be a microbe that was made sensitive to high temperatures so that it would not survive midsummer.

Bacteria

Recognizing that complete containment cannot be achieved, two working groups at the SPW inventoried methods that they indicated could be of use in controlling bacteria populations or the spread of their rDNA genetic information. Both groups recommended that, since no single risk management method could provide complete control, more than one method should be used. Some of the leading control methods follow.

Physical Controls

Physical methods to control bacteria are largely focused on the modes by which the organisms can be spread. Physical controls include the following methods:

- The dose should be kept as small as possible but high enough to produce an observable effect.
- Release can be timed to minimize dispersal; for example, calm atmospheric conditions should be sought.
- The site should be fenced or screened off to prevent the entry of larger organisms (for example, people, birds, and insects) that might carry the genetically engineered bacteria from the site. The use of a buffer zone can also reduce spread.
- Aerial dispersal can be reduced by choices of application methods and timing and by shelter belts, buffer zones, ground cover, moist soils, and cultivation practices.
- Dispersal from soil environments by water can be controlled by judicious selection of sites (slopes and soil characteristics), cultivation practices, grass buffers and perimeter barriers, and choice of irrigation methods.

Biological Controls

Biological control methods focus on selecting or constructing an organism to be vulnerable to a condition that will automatically limit it. The methods used or proposed for use are based on the selection of genetically engineered bacteria with characteristics such as

- sensitivities to chemicals that could kill them; extreme temperatures that would limit their seasonal survival; and starvation, predation, or parasitism that they might meet in a field site;
- a narrow niche (a range of environmental conditions in which it can survive);
- a specific requirement for a host that itself is vulnerable; and
- dependency on a specific, unusual nutrient.

Another proposal is to build "suicide genes" into engineered microorganisms. This is a term for a gene that would, either automatically or under some kind of external control by the manager of the process, destroy the organism after its intended function had been achieved. This approach has stirred some disagreement among scientists. While some have urged that it be pursued, others have pointed out that it is only suitable within a closely related group of microbes. They noted the extra difficulty of carrying out a second genetic engineering process to incorporate the suicide trait, in addition to the engineering done to transfer the originally desired trait.

Viruses

A number of distinctive features of viruses differ from those of bacteria. Scientists cite these features as particularly important to understanding how genetically engineered viruses could be controlled.

Physical Controls

Distinctive features of viruses and their implications for applying physical controls are described below.

- Viruses are more susceptible to physical conditions than are bacteria and other cellular organisms. Physical forces such as ultraviolet light, high temperature, and oxidation by air can be used as management tools.
- Since viruses are not mobile, limiting their spread requires controlling the availability of vectors to transport them. This involves restricting access to the site by people working on the test and organisms such as insects, nematodes, and fungi.

Biological Controls

Like physical control methods, biological controls are based on the nature of viruses, as illustrated below.

- Since a virus cannot reproduce except in a host, but may have other possible hosts besides the primary one intended in the test, the test system or location should offer no hosts, or at least as few hosts as possible, except the intended one.
- Viruses being engineered to serve as carriers for new vaccines can be weakened to reduce the probability of transmission.[2]

Plants

Genetically engineered plants or their genetic material might escape from a test area in two ways. One is through vegetative propagules, a term covering all kinds of nonsexual reproduction, including runners, bulbs, tubers, rhizomes, cuttings that root, and storage roots. These will be discussed in this section. The second, through sexual exchange with compatible species, via pollen release or the formation and escape of seeds, will be described in the next section dealing with transfer of genes.

Methods for preventing escape of vegetative propagules include the following:

- recover and/or eradicate the propagules;
- arrange for containment in the soil, possibly involving both above-ground and below-ground barriers to limit growth of the propagules or to block animal or bird access;
- recover propagules by soil screening after the test season; and
- sterilize the soil or use herbicides the following season (however, very few herbicides can affect underground vegetative structures).

Restricting Gene Transfer

A potentially important source of risk, beyond that due directly to the engineered organism itself, is the possibility that transferred genetic material may move beyond the organism into which it was engineered and lead to undesirable consequences caused by other organisms into which it may be transferred. There is wide recognition of this risk among scientists, and much rDNA work is done with the objective of limiting further gene transfer. However, given that an exchange of genetic material between two organisms may occur in nature through agents

[2]The leading example is vaccinia, which was itself used as the vaccine that eradicated smallpox. The technique calls for inserting one or more genes from the disease organism in question (for example, hepatitis B, malaria, and AIDS) into the chromosome of the carrier virus, at a location that can be chosen. In vaccinia, the site is in the middle of a particular gene, which is inactivated by being broken, weakening the vaccinia and thus making it less likely to spread.

originating outside the two, it may be impossible to completely avoid unintended gene transfer.

The transfer of genes from one individual organism directly to another, called horizontal transfer, is the main concern with bacteria. We found no information to indicate that viruses can transfer their genetic material to other organisms in ways that would give rise to another type of virus. Also, unlike bacteria, plants show no evidence of mechanisms to transfer genetic material directly from one organism to another, so that some risks of this kind are not of concern with plants. Gene transfer in plants, from two individuals to their offspring (in seeds), is referred to as vertical transfer.

Bacteria

Major methods to reduce the risk of unintended gene transfer in bacteria include

- disabling the plasmid[3] used to move the DNA in the original engineered transfer so that it will not be capable of initiating further transfers;
- inserting the transferred gene into the recipient bacterium's chromosome (the physical structure that contains genes), rather than leaving it on a plasmid;
- placing the inserted gene on a nonmobile plasmid if insertion on a site on a chromosome is not feasible; and
- selecting recipient bacteria that have no plasmids of their own and are free of several other features that can mediate gene transfer.

Plants

The usual mechanism of sexual reproduction in plants is by formation of seeds. If one parent is a genetically engineered plant, this would give rise to offspring that represent new plants that include the gene engineered into the original plant. Such breeding could occur with a range of other plants with which the engineered plant is cross-compatible (capable of producing fertile seeds), potentially transferring the introduced gene quite widely. The methods to control this vertical transfer center on either containing pollen or preventing the maturation or release of seeds.

[3]Smaller separate pieces of DNA, found in many species, are called plasmids, some of which can move from one bacterium to another. Certain plasmids serve as the vectors that carry DNA to new organisms in much of genetic engineering of bacteria.

Containing Pollen Escape

Biological techniques focus on reproductive barriers to limit and prevent the exchange of genetic traits. These include

- locating the test plot in geographic isolation from cross-compatible species,
- removing all cross-compatible plants from within the pollinating radius, and
- surrounding the test plot with a buffer zone of nonengineered plants that serve as a large pollen source, swamping out the pollen contributed by the test plot. However, if the buffer plants are allowed to set seed, they must all be removed completely to avoid release.

Physical techniques are more difficult and more likely to fail. Procedures include

- removing or blocking modes for pollen dispersal by bagging flowers, putting a pollinator-proof net over a field, planting test plot in an area free of pollinators, or treating plants with insecticide to control pollinators;
- "topping" plants, that is, cutting off reproductive structures before they mature; and
- avoiding unintentional dispersal of pollen by staff or on equipment by using dedicated equipment and clothing and protecting against theft or unauthorized intervention.

Preventing Seed Maturation or Release

Some of the above-mentioned techniques for preventing pollination can also prevent self-pollination, but pollination by surrounding plants, or even seed-developing without fertilization, is still possible. Therefore, even if pollination has been controlled, some attention must be paid to seed propagation. Control techniques include

- collecting mature seeds, capsules, or fruits (however, animals and birds can disperse unprotected seed structures);
- bagging all seed structure shortly after pollination; and
- introducing, or using plants that contain, self-incompatibility genes (genes that can prevent pollen of a given genotype from fertilizing flowers of the same genotype).

Monitoring

Many SPW participants thought that effective monitoring of the engineered organism and its rDNA should be a prerequisite to field testing. Monitoring is needed to track the success of containment. Evidence from monitoring that containment has not succeeded should trigger mitigation

actions, if harm could occur. Monitoring and mitigation should be considered in selecting the parent organism to be genetically engineered, constructing the engineered organism (particularly with microbes), and designing the field test.

In principle, monitoring of a genetically engineered organism can be done by tracking either the fate (that is, survival, growth, and dispersal) of the organism and its rDNA or its effects (the impact on the environment). In practice, however, an organism's effects may be undetectable for a number of reasons. Therefore, while experts encourage testing for effects and developing better tests, monitoring must concentrate on tracking the organism and its rDNA.

Experts discussed an effective sampling strategy, one that is adequate in time and space. The time (as well as spatial) extent of monitoring needed is dictated by the biology of the modified organism. With plants, for example, the seed dormancy time is a controlling factor. With microbes, measurements should continue until there is a stable or decreasing population that is unlikely to yield undesired effects. This may necessitate monitoring for more than a year (or at least include a sample from the following year) to take account of seasonal effects.

Some spatial issues apply mainly to microbes with less relevance to plants. For example, it is necessary to monitor genetically engineered microbes in soils involved in field tests, not just on host organisms. Soils offer a wide variety of conditions to support microbes in a number of different subhabitats. Viruses can be harbored in soils, in some cases for many years. Monitoring of subhabitats may indicate whether the microbe in question will survive and grow into a large population ("bloom") in other natural environments.

Monitoring should be carried out with attention to possible modes of transport of the engineered microbes from soils, on animal and insect vectors, by leaching, in water runoff, on winds, and by erosion carrying material off in surface waters. It must also cover buffer areas around test sites and possible transport from the site by the experimenters themselves.

Detectability Limits With Microbes

To monitor an engineered microorganism effectively, researchers must know its threshold level of detectability. The complete elimination of a microbe, called die-out, cannot be proven by available monitoring methods in a natural environment such as soil. The lowest detectable levels of

bacteria are in a range about 10 to 30 organisms in a gram of soil that typically holds about a billion organisms. Thus, available monitoring methods can identify microbes at a very low detection limit, in the best case about 1 in 100 million. Even so, a microbe could drop to a population below the detection limit, called die-back, but remain present and able to bloom later.

Because die-out cannot be established with certainty, a suggested alternative method is to monitor population trends. This involves comparing the numbers of an engineered microbe, after it has reached a steady-state population, with those of its normal parent microbe under the same conditions. If the engineered organism's population is lower than the population of its parent, it could be judged less competitive and probably of lower risk, whereas a higher population might represent a higher risk.

For some cases in which population monitoring might not be successful, an alternative approach would be to monitor for unplanned, unexpected ecological impacts of the organism. Observation of potentially sensitive organisms, such as insects, could reveal harmful impacts; the absence of such impacts would suggest that control methods are effective. Other observations for ecological effects that may be appropriate include community variables, such as groups of organisms rather than single species; levels and flows of particular nutrients; and system-level variables, such as species diversity and rates of chemical processes (for example, nitrogen fixation or carbon uptake).

Monitoring Techniques

For most organisms two classes of monitoring techniques are possible. The traditional techniques track the engineered trait, or another trait for which the organism was deliberately selected or bred, called a marker. The marked organism is detected by some biological property determined by the marker trait. This may be an ability to grow on an unusual carbon source, resistance to a particular substance usually harmful to the organism, or a wide range of other traits, for example, production of a compound detectable by a color test. This class of methods is capable of great sensitivity (as high as the previously noted 1 in 100 million) and can be used routinely without complex new laboratory procedures.

The other class of methods potentially offers the important advantage of being more specific. These newer techniques are based on biological processes such as antibody binding or modern laboratory procedures.

Examples of the latter include gene probes and mapping of DNA fragments produced by controlled cutting of the chromosome into fragments by certain enzymes. Compared with marker traits, they are less sensitive, are often slower, and require advanced laboratory procedures that currently bar their use on a routine basis.

Finally, some monitoring techniques and concerns are specific to separate groups of organisms. The widest range of techniques is potentially applicable to bacteria. Many of the monitoring methods have significant disadvantages, such as instability, poor sensitivity, and high costs. Therefore, some precautions and improvements may be necessary.

Bacteria

The monitoring technique generally judged most sensitive, the detection of marker traits, was originally developed in the study of bacteria. Some of the most sensitive and widely used markers are based on the bacteria's ability to resist one or more antibiotics included in selective growth media.

Some of the newer techniques mentioned earlier can also be useful with bacteria. Particularly useful for tracking specific rDNA are the techniques of mapping enzymatically produced DNA fragments and colony hybridization combined with gene probes. Gene probes are specific for detecting the gene being tracked and have the best potential for following it and giving unambiguous identification.

Another new technique is the use of antibodies to the engineered bacteria, or to the protein produced by its rDNA, which have fluorescent groups attached. While these are of relatively low sensitivity, they can make it possible to detect the engineered microbe, or its rDNA, under a microscope.

Lastly, the technique of placing some set of sentinel plants, chosen to be very sensitive to the genetically engineered bacteria, in or around the test area is also recommended to make it possible to get more complete risk information from field testing.

Viruses

The main method for detecting a virus in the field is to inoculate a host organism with field material to see if it can infect an untreated host. Measurements should also be made to see if the virus can be found replicating in hosts when the field test is presumed to be finished. To monitor for the virus escaping from the test site, researchers can place contained

hosts at locations surrounding the site, to see if they become infected. Finally, to monitor the genetic stability of the virus, experts regard one of the newer techniques as the best: performing DNA analysis (gene probes) on samples of virus that are amplified in a host after having been collected in the field.

Plants

A visual examination of the area surrounding a test plot should indicate whether seeds or other propagules have escaped from the site and sprouted. However, this judgment can be made only if the area surrounding the site was shown to be free of the test species before the field test was started.

For detecting possible genetic exchange with other plants, a simple method is to observe the form of progeny grown from the seeds produced and compare them with the engineered plant. However, several of the newer molecular tests can be used without waiting for a full plant generation to grow. These include marker-gene methods with DNA hybridization tests, as well as mapping of enzymatically produced DNA fragments, or markers depending on isozymes, which are varying forms of certain enzymes found in different strains of organisms.

Mitigation

The SPW concluded that no environmental testing should occur without available mitigation methods. These methods are to be used if a field test needs to be ended early for any reason or if it is necessary to eliminate the experimental organisms or others to which they may have transferred genetic information after a field test is over. Particularly with genetically engineered microbes, extensive monitoring should also accompany mitigation to determine its effectiveness and the extent of spread of the genetically engineered organism.

Bacteria

As with controls on survival, multiplication, and spread, no single mitigation method is likely to be completely effective with bacteria, so more than one should generally be used. Mitigation methods include

- fumigating the site with antibacterial compounds such as methyl bromide;
- applying extreme temperature and pressure (which can be difficult in a field setting);

- adjusting chemical conditions outside of the genetically engineered microbe's (or host's) range of tolerance, for example, adjusting the acidity;
- removing hosts; and
- physically isolating the infected site.

Viruses

Mitigation methods, to be used if the controls have failed or if the test virus shows undesirable properties, largely have the same basis as controls. They include

- eliminating natural hosts and any vectors that could transport the virus elsewhere;
- eliminating the virus itself from the site, with particular attention to its usual environmental reservoirs such as soil and dead plant material; and
- killing essentially everything alive on the site, plus nearby plants that might harbor the virus, and sterilizing the soil or paving over the site.

Plants

Mitigation methods include

- applying herbicides (but more than one may be needed, especially if the test trait is a herbicide-resistance);
- destroying the physical habitat, for example, burning the field;
- pulling the plants up, if the number of plants is limited; and
- making a gene addition that will render the plant susceptible to a specific control agent, such as a chemical (a theoretical method that is not yet available).

Managing Risks of Accidental Releases From Laboratories and Fermentors

Concerns about the use of genetically engineered organisms include not only their deliberate but also their accidental release. In this report, we have focused on the management of risks associated with deliberate releases. In this appendix, we review risk management mechanisms designed to prevent accidental releases of genetically engineered organisms from containment, especially from research laboratories and fermentation facilities. Potential harm to people or to the environment from an accidental release of such organisms during research activities or the recombinant DNA manufacturing process—via wastes, air emissions, exposed workers, or other means—is the principal concern. Industry representatives, government officials, and scientists, however, believe that regulations governing laboratory and fermentor containment provide adequate assurance of safety. The following discussion summarizes the basic guidelines regulating research laboratories and fermentors. It also comments on the concern about genetically engineered organisms escaping from containment.

Role and Regulation of Laboratories and Fermentors

Laboratories and fermentation facilities make use of genetically engineered microorganisms for various purposes. They are heavily involved in both research and production connected with genetically engineered organisms and products. Government, university, and private laboratory researchers use such organisms in developing products with potential applications to a wide variety of activities, including agriculture, pharmaceuticals, mining, and the degradation of toxic wastes. For agricultural purposes alone, hundreds of research projects involving such organisms are underway in laboratories across the country.

Similarly, these organisms have begun to play an increasingly important role in the fermentation industry, where they have contributed to current production. They have already been used to manufacture rare drugs in larger quantities at lower cost than could be achieved by conventional techniques. Fermentors using them are also expected soon to be producing valuable products such as foods, pharmaceuticals, vitamins, enzymes, pesticides, plastics, and a broad range of organic chemicals.

The federal regulation of these activities occurs primarily through "Guidelines for Research Involving Recombinant DNA Molecules" developed by the National Institutes of Health Recombinant DNA Advisory Committee (NIH-RAC). As the title indicates, the guidelines focus on rDNA rather than on all techniques of genetic engineering. The guidelines provide standards for the physical and biological containment of these rDNA

organisms. Physical containment refers to the use of laboratory practices, equipment, and design; biological containment limits the abilities of organisms (or parts thereof) used in genetic engineering to survive and transmit their novel traits outside the laboratory. In particular, the guidelines define four biosafety levels (BL) of physical containment, ranging from BL1, the least stringent, to BL4, the most stringent, and two levels of biological containment. Compliance is mandatory for all federally funded laboratory research and fermentation activities. Although NIH has asked nonfederally funded researchers to comply on a voluntary basis, several state and local governments require such compliance.

Along with NIH, FDA is involved in overseeing the use of rDNA organisms in fermentation facilities. All manufacturers of new drugs and biologics must conform with FDA's Current Good Manufacturing Practice regulations. These are designed to protect the integrity and purity of the product by requiring adequately equipped manufacturing facilities and trained personnel, stringent control over the manufacturing process, and appropriate finished product examination. In addition, FDA has issued a document entitled "Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology," which provides suggestions for evaluating the safety, purity, and potency of such products. Since FDA's regulations are concerned with controlling product quality rather than containing of genetically engineered microorganisms, our discussion focuses on the NIH guidelines.

Guidelines for Laboratories

The NIH-RAC developed and published its guidelines in 1976 and has revised them many times since then. The guidelines state that they can never be complete or final, since all conceivable experiments involving rDNA cannot be foreseen. The current guidelines were issued in May 1986.

The primary objective of the guidelines has been the prevention of harmful accidental releases. They prescribe the incremental measures to be taken as the perceived risk of the organism increases. When genetically engineered organisms considered potentially dangerous are used in laboratory or fermentation activities, specific controls are required to deal with each of the major modes of potential escape from containment.

Physical Containment

In the guidelines, appendix G ("Physical Containment") summarizes standard laboratory practices and training; it also provides information

on the four levels of containment. The appendix states that the first principle of containment is strict adherence to good microbiological practices. Such adherence entails (1) a training program in sterile techniques and the biology of the organisms used in the experiment, (2) an emergency plan that describes the procedures to be followed if an accident contaminates personnel or the environment, (3) the availability of a vaccine if work is being conducted with a known pathogen, and (4) serological monitoring (for example, blood tests), if appropriate.

The four physical levels can be summarized as follows:

- BL1 is the minimal safety level for equipment and facilities used in teaching laboratories where work is done with defined and viable strains of microbes not known to cause disease in healthy adults.
- BL2 practices are applicable to those facilities in which work is done with indigenous moderate-risk agents present in the community and associated with human disease of varying severity. With good containment techniques, activities can be conducted openly in the laboratory, provided that aerosol emissions are low. Neither BL1 nor BL2 is intended to provide complete containment.
- BL3 is the first of two contained levels. The practices are applicable to those facilities where work is done with indigenous or exotic agents, the potential for infections by aerosols exists, and the diseases may have serious or lethal consequences.
- BL4 is used for dangerous and exotic agents where use presents the risk of life-threatening disease. All manipulations are carried out under conditions of maximum containment, that is, special physical construction, personnel uniforms, and other arrangements.

The appendix states that physical containment is achieved through the use of laboratory practices, containment equipment, and special laboratory design. Emphasis is placed on primary means of physical containment, provided by laboratory practices and containment equipment. Special laboratory design provides a secondary means of protection against the accidental release of organisms outside the laboratory or to the environment. Special laboratory design is used primarily in facilities in which experiments of moderate to high potential hazards are performed.

In addition to the NIH guidelines, a book published jointly by NIH and the Centers for Disease Control provides detailed information on containment measures for laboratory research. Scientists consider the book,

Biosafety in Microbiological and Biomedical Laboratories,[1] the "bible" for laboratory research. It discusses containment in reference to laboratory practices and techniques, safety equipment, and facility design. It refers to the "basic laboratory" as one that conforms with BL1 and BL2 criteria. A "containment laboratory" must comply with BL3 standards. The "maximum containment laboratory," only one of which is currently in operation (a federal facility in Frederick, Maryland), meets BL4 criteria.

Biological Containment

In addition to rules for physical containment, the guidelines contain appendix I, "Levels of Biological Containment." It states that any combination of vector (a molecule, such as a virus, for carrying the DNA) and host (the cell to which the rDNA is to be transmitted) must be chosen or constructed so that escape from the laboratory is minimized. Two levels of biological containment, host-vector 1 and 2 (HV1 and HV2), define a moderate and high level of containment, respectively. HV1 systems other than those already approved by NIH, and all HV2 systems, must be specifically reviewed by NIH-RAC and certified by the Director, NIH.

Guidelines for Fermentors

The NIH guidelines also contain appendix K, "Physical Containment for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules." It has served as the source of standards for government, university, and industry fermentors larger than 10 liters. Appendix K defines three levels of containment (BL1 through BL3) for large-scale research or production. It specifies progressively more stringent measures to reduce or prevent the chance of escape. The biosafety level concept for fermentors is similar to that used for laboratory research, but appendix K is oriented specifically to fermentation facilities.

Certain rDNA organisms, including specific types of bacteria and yeast used in fermentation processes, are exempt from NIH-RAC review. These exempt organisms are considered the "workhorses" of the fermentation industry and account for the vast majority of all production. BL1 containment standards must be applied when these organisms are used.

NIH is considering a proposal by FDA that appendix K containment standards for these organisms be relaxed. BL1 is stringent, compared with

[1]Centers for Disease Control and National Institutes of Health, Biosafety in Microbiological and Biomedical Laboratories, HHS Publication No. (CDC) 84-8395 (March 1984).

what industry routinely requires of its fermentors for non-rDNA organisms. As a result, in February 1987, FDA recommended that appendix K be relaxed for the rDNA organisms already exempt from NIH RAC review. The proposal is mainly intended to allow industry to move from BL1 standards for exempt rDNA organisms to the lower level of containment.

Such a shift would be consistent with the conclusions of a report on genetic engineering issued by the Organization for Economic Cooperation and Development, a group established to coordinate the economic and social policies of 24 industrialized countries. This organization studied rDNA-related issues and found that the vast majority of industrial rDNA large-scale applications will use organisms of intrinsically low risk, which warrant only minimal containment.

One concern about the guidelines is that they are primarily intended to cover research activities, not industrial production. As a result, some industrial issues may not be addressed. For example, the guidelines do not address the issue of an extremely large, accidental spill from a fermentor. According to federal officials and an industry spokesman, however, the fermentation industry has adapted the guidelines to apply to large-scale production. They told us that the industry has not only complied with the basic intention to prevent harmful releases but has also adopted novel ways to contain the organisms used in fermentation activities and additional technical measures to decontaminate its genetically engineered products.

Implementation of the Guidelines

Responsibility for implementing the guidelines resides with local Institutional Biosafety Committees (IBC's) established by universities and companies involved with rDNA research. IBC's consist of no fewer than five members selected for their experience with rDNA technology; at least two members are to represent the interests of the surrounding community with respect to protection of health and the environment. They are to be established by any public or private institution conducting rDNA research and development. More than 300 have been established across the nation.

The guidelines divide experiments into four classes and define the respective duties of the NIH RAC and the IBC's with regard to each of them. The classes are

- experiments that require specific RAC review and NIH and IBC approval before initiation,

- experiments that require IBC approval before initiation,
- experiments that require IBC notification at the time of initiation, and
- experiments that are exempt from the procedures of the guidelines.

In the first two categories, depending on the specific experiment, NIH or the IBC is responsible for setting the appropriate containment standard, from BL1 to BL4. All experiments in the third category can be carried out at the BL1 containment level.

There is some disagreement about the effectiveness with which the guidelines are implemented for laboratory research. A leading university microbiologist, for example, cited a disregard for safety in many laboratories practicing rDNA research, whereas an NIH official deems such criticism overstated.

Two of the most critical remarks were made at a 1985 conference on Biotechnology and the Environment sponsored by EPA. The Director of Biotechnology for a major chemical company expressed the opinion that widespread disregard for safety could be found in most university rDNA research laboratories and many companies as well. The microbiologist mentioned above echoed this concern, stating that probably few facilities for containment of microorganisms have never had an accident, including the best facilities in the United States. He added that most university laboratory personnel are not well-trained for handling potentially hazardous organisms or do not take the risks particularly seriously, resulting in a high probability of release.

An EPA official generally agreed with these statements. He said that the problem of careless laboratory procedures results from an attitude in which familiarity with the organisms involved has bred complacency. He said that in all probability, rDNA materials are being washed down laboratory drains without personnel's taking adequate measures to decontaminate them.

The Director, Office of Safety and Health, NIH, however, told us that these criticisms may be overstated. He said that for the past several years, rDNA laboratory research has used organisms widely considered harmless and exempted from NIH-RAC oversight on the basis of extensive risk assessment data showing that they are benign. To the extent that some laboratory research may be conducted carelessly, it generally involves these exempted organisms. In the less frequent instances where potentially harmful organisms are used for research purposes, he feels,

researchers recognize the risks and take the necessary precautions to maintain safety.

Level and Management of Risk

Even with the proper implementation of the NIH-RAC containment guidelines, some microorganisms are believed to escape from laboratories and fermentors. Such escape is more likely to occur at the lower levels of containment. For example, a molecular biologist experienced in risk assessment discussed potential breaches of containment in quantitative terms for BL1 laboratories and fermentors and stated that scientists have identified several basic modes of escape: airborne emissions, waterborne escape, solid wastes (such as lab coats, gloves, and glassware), and technicians' clothes and skin.

She also reported[2] scientific estimates that, on a daily basis, 200 million to 4 billion microorganisms escape from a laboratory with a BL1 rating. (Her results further suggested that between 1,000 and 10,000 times as many microorganisms would be released from containment during a field trial on a plot of land as small as 0.2 acres.) She reported additional research estimating that, on a daily basis, 700 to 900 trillion microorganisms escape from a 250 liter fermentor at BL1. (A 250 liter fermentor is extremely small for industrial purposes; fermentors of 2,000 to several hundred thousand liters are used for most production.) These numbers are sensitive to several assumptions and are questioned by federal officials.

Quantitative estimates of organisms escaping from containment, even if correct, must be balanced against the unlikelihood of any resultant harm. Taken by themselves, such estimates are not particularly significant. The organisms used for genetic engineering at the BL1 level are well known and generally considered harmless. Even if large numbers are released in a spill from a fermentor, they would not be likely to survive outside the immediate area and even less likely to cause harm. By contrast, even one tuberculosis microbe released from a laboratory, given its ability to multiply and infect, can pose a major risk. The issue of concern is the inherent risk associated with an organism, not the genetic engineering by which it is produced or the occurrence of a small-scale, accidental release of a harmless organism.

[2]See Harlee S. Strauss, "How Many Microbes Really Constitute Environmental Release?" Bio/Technology, vol. 5, March 1987, pp 232-237.

The Director, Office of Recombinant DNA Activities, NIH, said that some microorganisms may leave the laboratory, for example, on technicians' clothing, but stated that these microorganisms are unlikely to survive, multiply, and result in harm. He said that in more than a decade of research using rDNA organisms, no known harm resulting from any accidental releases of rDNA organisms into the environment has occurred. The Special Assistant to the Administrator for Biotechnology, FDA, said that such releases can more accurately be termed incidental, not accidental.

Industry representatives and federal officials and scientists believe that although some releases of genetically engineered organisms may occur, such occurrences do not pose a serious hazard to human health or the environment. They stress the need to distinguish between harmless and harmful accidental releases. In particular, they say that most fermentation processes pose little risk because the organisms grown in these facilities are not capable of living in the environment. However, additional steps are being taken to reduce this risk when genetically engineered organisms are involved. Overall, they believe that containment levels are consistent with the level of perceived risk and are set to prevent the release of harmful organisms.

An official with the Industrial Biotechnology Association, a trade organization whose 75 members are engaged in biotechnology applications in various fields, focused his comments on the fermentation industry. The industry is working at basically a pilot plant level with genetically engineered microorganisms, using fermentors of 1,000 liters or less. Although the industry believes that these organisms pose no serious hazards, it is working at such a small scale in part as a precaution to reduce the chance for escape. The industry has also taken special steps to inactivate the organisms either chemically or physically. As a result, no problem with waste disposal of genetically engineered microorganisms is believed to have occurred. Eventually, many fermentation products using genetically engineered microorganisms will be disposed of in a conventional manner at water treatment facilities.

In general, the fermentation industry believes that it is sensitive to the various levels of risk in its activities. For products such as food enzymes, which have been found to pose no danger to workers or the general population, containment standards are low. For vaccines and other products involving known pathogens, containment standards are more stringent. The highest possible containment level for fermentors has been applied to protect workers and manage the waste by-products

associated with certain hazardous drugs for treating cancer. These drugs are not produced by means of genetically engineered microorganisms, but they provide an example of the extreme containment measures applied whenever the level of risk warrants such precautions.

In contrast to this confident outlook for managing risks within the fermentation industry, some scientists have expressed concern about potential problems arising from waste products containing live, genetically engineered microorganisms. Biological waste resulting from large-scale biotechnology processes using genetically modified organisms is largely unregulated. Although some companies have adopted state-of-the-art techniques of sterilization, inefficient sterilization practices are common in the treatment of all waste forms. In response to these concerns, EPA is preparing a nationwide survey of industry focusing on potential problems associated with bioengineered waste and the efficiency of treatment technologies.

Appendix III

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Comments From the Department of Agriculture

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

DEPARTMENT OF AGRICULTURE
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WASHINGTON, D.C. 20250

MAR 1 8 1988

Mr. J. Dexter Peach
Assistant Comptroller General
Resources, Community, and Economic Development Division
U.S. General Accounting Office
Washington, DC 20548

Dear Mr. Peach:

The U.S. Department of Agriculture (USDA) appreciates the opportunity to comment on the U.S. General Accounting Office (GAO) draft report, Biotechnology: Managing the Risks of Field Testing Genetically Engineered Organisms, dated February 1, 1988.

This ambitious and comprehensive report, which summarizes a great deal of scientific, technical, and legal information, is generally positive about the Federal agencies' efforts to manage the risks of field testing genetically engineered organisms. The study provides a valuable analysis of the procedures used by USDA, the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA) to regulate deliberate releases of the products of the new technology. However, GAO recommends "some modifications to agency policies in order to narrow gaps in regulatory coverage," and "that USDA strengthen its regulation of potential plant pests . . . by not exempting . . . those organisms created by transfer of a certain type of genetic material" (pp. 5-6). As stated below, USDA does not feel that the recommended modification is necessary based upon a consideration of the limited nature of the exemption and a review of scientific opinion and the scientific literature.

See comment 1

The USDA comments on the draft report are confined to (1) the GAO analysis of USDA's procedures for managing risk and its recommendations for modifications, and (2) changes suggested for the USDA material, presented by page, and included as an enclosure to this letter.

1. GAO Analysis and Recommendation

After analyzing the laws, regulations, and policies used by Federal agencies to manage the risks of environmental releases of genetically engineered organisms, GAO concluded that "the agencies' regulatory authorities and policies are generally appropriate, but we also found gaps in authority and product coverage" (pp. 28-29). The report then makes recommendations for narrowing gaps in regulatory coverage.

The GAO recommendations are based on criticism of both EPA and USDA for subjecting certain categories of genetically engineered organisms to more or less stringent review, or to exemption from review, on the basis of certain biological features (p. 48). In the case of USDA, GAO disapproves of the

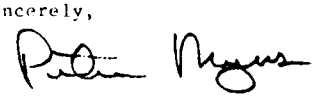
exclusion contained in Title 7 of the Code of Federal Regulation, Part 340 (7 CFR 340) for recipient microorganisms that are not plant pests and have resulted from the addition of genetic material that is well characterized and contains only noncoding regulatory regions (52 FR 22896-22897, June 16, 1987, hereinafter "final rule").

An exclusion for microorganisms that are nonpathogenic, noninfectious, and not a plant pest, and that have resulted from the addition of noncoding regulatory regions was included in the proposed version of the final rule (51 FR 23307, June 26, 1986). The exclusion was retained in the final version of the rule after a thorough consideration of safety issues, a search of the scientific literature, and an analysis of the comments on the issue. A discussion of the issues and the comments are contained in the Preamble to the final rule.

In its criticism of the exclusion, GAO discusses the comments of the Ecological Society of America and the American Society for Microbiology sent to USDA on the proposed rule. USDA feels that GAO has not fully considered the comments of either organization. The Ecological Society of America recommended that the exemption be narrowed "so that it applies only to prokaryotic organisms," which is what USDA has done. In the case of the American Society for Microbiology, the statement is made that the Society favors examining some of the cases involving regulatory sequences, "such as those in which foreign regulatory sequences are joined to genes with potentially harmful or disruptive gene products." USDA agrees with the Society, and has specified that the exclusion does not apply to plant pests, i.e., those that produce harmful or disruptive products.

In summary, USDA believes that its exclusion is safe and appropriate because it applies only to recipient microorganisms that are not plant pests, and because the transfer of well characterized noncoding regulatory regions to such a host does not create a gene product which did not exist prior to the acquisition of the new genetic material. In our opinion, the scientific literature and scientific opinion support this limited exclusion. Based upon a review of the evidence presented to date, USDA does not feel the exclusion should be reconsidered.

Sincerely,



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ACTING SECRETARY

Enclosure

The following are GAO's comments on the Department of Agriculture's letter dated March 18, 1988.

GAO Comments

1. The suggested changes to the draft outlined in the enclosure to the comment letter were mainly of a technical nature. These have been evaluated and included where appropriate.

Comments From the Environmental Protection Agency

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR [illegible] 1988

OFFICE OF
POLICY, PLANNING AND EVALUATION

Mr. J. Dexter Peach
Assistant Comptroller General
Resources, Community, and Economic
Development Division
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Peach:

On February 1, you sent a General Accounting Office (GAO) draft report to the Environmental Protection Agency (EPA) for review and comment. The report is entitled "Biotechnology: Managing The Risks Of Field Testing Genetically Engineered Organisms" (GAO/RCED-88-27). As required by Public Law 96-226, the Agency provides the following comments.

The issues raised by the report concerning the types of microorganisms that should be regulated by the Agency have also been raised by other parties; for example, in public comments on the Agency's proposed policy on regulation of biotechnology products described in the June 26, 1986, Federal Register.

The Agency has been actively evaluating these issues as part of the process of developing proposed rules under the Toxic Substances Control Act and amending the Federal Insecticide, Fungicide and Rodenticide regulations to fully implement its approach to regulation of biotechnology products.

The issues raised in the GAO report will be addressed by EPA in its proposed rules.

In closing, I would like to emphasize the evolving nature of the debate on regulation of biotechnology products and the likelihood that this debate will affect the outcome of EPA's current rulemaking effort. Indeed, EPA's internal approach to biotechnology regulation has been subject to considerable change since the issuance of the 1986 policy statement.

Changes will undoubtedly continue to occur as rule development proceeds. The GAO report should recognize that biotechnology policy will continue to evolve as our scientific knowledge increases.

I appreciate the opportunity to comment on the draft report.

Sincerely,

Linda J. Fisher

Linda J. Fisher
Assistant Administrator

Comments From the Department of Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

MAR 15 1988

Mr. Lawrence H. Thompson
Assistant Comptroller General
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Thompson:

Enclosed are the Department's comments on your draft report, "Biotechnology: Managing the Risks of Field Testing Genetically Engineered Organisms." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard P. Kusserow
Inspector General

Enclosure

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GENERAL ACCOUNTING OFFICE'S (GAO) DRAFT REPORT "BIOTECHNOLOGY: MANAGING THE RISKS OF FIELD TESTING GENETICALLY ENGINEERED ORGANISMS," RCED 88-27, February, 1988.

We appreciate the opportunity to provide comments on this draft report. We believe that while the report has some strengths (its factual description of the mechanisms of risk assessment and risk management by the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and United States Department of Agriculture (USDA), for example), it has numerous serious deficiencies that lead to unsupportable conclusions and recommendations.

See comment 1.

1. The draft report erroneously separates genetic engineering using recombinant deoxyribonucleic acid (rDNA) techniques from older, more "traditional" methods of genetic engineering; however, this is not clear since the report nowhere defines genetic engineering. Actually, recombinant DNA techniques are merely the newest refinement in the continuum of genetic engineering methods. This view is supported by world-wide consensus as expressed by such prestigious scientific bodies as the Organization for Economic Cooperation and Development (OECD), a North Atlantic Treaty Organization (NATO) experts group, the SCOPE/COGENE working group, the International Institute for Cooperation in Agriculture Working Group (IICA), the National Institutes of Health Recombinant DNA Advisory Committee (NIH RAC), and the U.S. National Academy of Sciences (NAS).

As merely the newest genetic engineering technique, the rDNA process of creating new organisms is not inherently more dangerous than older techniques that have produced, among others, live vaccines such as those for measles, rubella, yellow fever, polio, and influenza.

See comment 2

2. The draft report repeatedly states that there has been very little experience in addressing genetic engineering products and processes. It is upon the basis of this misunderstanding that GAO reaches its conclusions and makes its recommendations. In fact, the organisms such as the live vaccines mentioned above are genetically engineered, albeit by older techniques, and have provided a long history of experience in creating, regulating, and introducing organisms that not only are genetically engineered, but also have the potential to do significant harm if not controlled properly. These and other genetically engineered products have been safely and successfully used for many years. Other examples of successful introduction of genetically engineered products are the extraordinary safety record of field testing live microbes as pesticides and for other purposes prior to the recent imposition of Federal regulation. Hundreds of such products are currently in use in a variety of commonly used pesticides and other products.

See comment 3.

3. The report focuses upon the technique (or process) of creating new organisms rather than the characteristics of the new organism. In this way, it fails to distinguish between those issues that are unique to release of genetically engineered (specifically, rDNA-derived) organisms and those issues that are common to release of any organism. The latter include unmodified organisms as well as such well known and benign "genetically engineered" organisms as new breeds of cattle, dogs, flowers, corn, wheat, and so forth. As a result, some of the conclusions would, if applied literally, significantly and unnecessarily increase governmental oversight of traditional environmental experiments, traditional plant and animal breeding, and the development of new approaches to environmental problems.

The scientific community has reached a broad consensus that the proper focus for controlling introduction of genetically engineered organisms is the product itself rather than the process by which it came into being. Both the NIH criteria for determining the level of concern regarding new organisms and the recent policy statement by the NAS (among many others) recognize this approach and support it. The NAS statement is perhaps the clearest and most succinct of the numerous such statements. It states that: (1) R-DNA techniques constitute a powerful and safe new means for the modification of organisms; (2) genetically modified organisms will contribute substantially to improved health care, agricultural efficiency, and the amelioration of many pressing environmental problems that have resulted from the extensive reliance on chemicals in both agriculture and industry; (3) there is no evidence that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms; (4) the risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods; and (5) the assessment of risks associated with introducing rDNA organisms into the environment should be based on the nature of the organism; based on the environment into which the organism is to be introduced; and be independent of the method of engineering per se.

In concentrating upon the process rather than the product, the report perpetuates the misapprehension that genetically engineered products are significantly more hazardous than other products and therefore must be much more rigidly controlled. We would contend that products -- whether genetically engineered or not -- should be subjected to regulation commensurate with their potential to do harm rather than the process by which they are made.

See comment 4.

4. The draft report ignores or discounts the body of scientific knowledge that supports the ability of experts to make accurate and useful predictions (risk assessments) about the characteristics of organisms, new or old, genetically modified or not. As noted

elsewhere, viral vaccines produced with older genetic engineering techniques have been dramatically effective throughout the world; they are rivaled only by the agricultural "green revolution" (a result of genetically engineered plants) as a promoter of human longevity and quality of life. The fruits of this older, "conventional" genetic engineering have been tested and developed in an atmosphere of minimal regulation that has stimulated innovation. Innumerable microbes have been subjected to testing in unregulated small-scale field testing -- small-scale trials were exempt from both the Federal Insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act until recently -- boasting an admirable safety record. The scientific method and prior experience do enable us to make useful predictions. The newest genetic engineering techniques are already providing still more precise, better understood, and more predictable methods for manipulating the genetic material of microorganisms. It should be noted that the basis of our ability to make predictions about risk and safety is dual: knowledge of the biological precursors ("parent(s)") of an organism; and the sequential nature of testing prior to even a small-scale field trial. This latter point is important because the testing in the laboratory, growth chambers, growth rooms, and greenhouses that precedes field trials can provide important and unequivocal data about the limits of behavior of new strains or cultivars. This tiered, sequential approach is and has long been integral both to scientific and commercial endeavors.

See comment 5.

5. The report reflects a misunderstanding of the concept of "case-by-case." GAO uses the concept invariably to mean "every case," in the sense that case-by-case evaluation means that every proposed test should be subject to government evaluation and approval. This is not the view of case-by-case used by the agencies and others.

Until recently, small-scale field trials of pesticides and other organisms such as Rhizobium, Thiobacillus, or new strains of marigolds were exempt from governmental regulation. Even under the most stringent proposed regulations, small-scale testing of "intrageneric" or self-cloned organisms would be effectively exempt from EPA's jurisdiction. The testing of animals and plants is virtually completely exempt. Case-by-case review/regulation as practiced by the regulatory agencies and endorsed by OECD, NAS, and others is quite different. In its landmark 1986 report, OECD defined case-by-case as "an individual review of a proposal against assessment criteria which are relevant to the particular proposal." They went on to add this qualifier, "this is not intended to imply that every case will require review by a national or other authority since various classes of proposals may be excluded." U.S. Federal agencies have, in fact, generally followed through on applying these principles. Thus, an investigator contemplating a field trial reviews or compares the various aspects of an experiment to relevant assessment criteria to determine whether prior governmental approval is required. For

example, if the experiment were a field test of ore extraction by an indigenous Thiobacillus manipulated with rDNA techniques in order to delete a gene, the review performed by the investigator would reveal that the relevant EPA regulations under the Toxic Substances Control Act exempt the experiment from prior approval. This is the context of FDA Commissioner Young's remarks quoted by GAO on p. 46. He was not calling for "every case" evaluation under current practice in the U.S.

The OECD qualification of case-by-case reiterates the important principle that categories of products entailing negligible or trivial risk may be defined that do not require special governmental scrutiny or restriction; these could conceivably range from narrow (for example, an inclusive list of such organisms as Pseudomonas syringae, Bacillus Thuringiensis, and Thiobacillus ferrooxidans, manipulated by self-cloning) to broad (for example, all well-characterized non-pathogens).

See comment 6.

6. The draft report is inconsistent in that it both approves of the NIH-RAC approach of developing generic guidelines that progressively exempt groups of experiments and criticises USDA and EPA for applying this principle even more conservatively. We submit that the NIH-RAC approach is equally valid for agencies' following the RAC lead as well as reducing the stringency of regulation of self-cloned organisms in appropriate situations.

The exemptions in the current NIH Recombinant DNA guidelines are based on two principles:

(1) The host organism is sufficiently well understood and sufficiently unlikely to become a dangerous pathogen to allow the introduction of new genetic information within the laboratory without special oversight. This type of exemption, for which organisms are listed in Appendix A of the current NIH guidelines, may not be relevant for release of genetically engineered organisms, as stated on p. 49 of the draft report. In fact, such releases are not exempt from NIH review.

(2) The engineered organism does not differ qualitatively from organisms formed by natural means, either in the laboratory or in the environment. This sort of exemption recognizes the principle, referred to repeatedly in the draft report, that genetic engineering per se should not lead to a higher level of concern about a particular organism, but that the nature of the final organism itself should be the paramount consideration. Thus, organisms which have been manipulated in the laboratory by new techniques to give a result not different from that achievable by classical techniques do not warrant regulatory scrutiny beyond what would be appropriate to the classically-derived organisms.

Even some "unique" organisms, which are unlikely to arise in nature, may be categorized as of low or negligible risk to human health or the environment; examples of these are E. coli, B. subtilis, and Saccharomyces manipulated with rDNA techniques to produce pharmaceuticals such as human insulin or interferon; or Rhizobium with hyperfunctioning nif genes and containing an SV40 promoter.

It is our opinion that the EPA and USDA exemptions of particular organisms from special oversight reflect this second principle, and that this is a legitimate basis on which to make exemptions from oversight, particularly for small-scale releases. For instance, the USDA exemption for "non-coding regulatory sequences" should not lead to expression of an entirely new product within a given cell. We know from many years of genetic research that spontaneous and induced mutations which change the level of expression of genes can and do arise in the environment. While such changes may well change the properties of a given organism, they have not been subject to special regulation for small-scale testing up to this time. Similarly, the EPA exemption of intra-genetic exchanges between non-pathogenic bacteria is based on the concept that such exchanges already occur in nature and, therefore, will not represent a unique and totally new introduction into the environment.

The issue presented here speaks against the suggestion, on pp. 49 and 50 of the draft report, that the NIH guideline exemptions are somehow not relevant to releases. While exemptions of the first category may not be relevant (although the principle should be applicable, with different sorts of constraints used to develop a list), exemptions of the second category should be.

Finally, we disagree with the GAO suggestion that the USDA exemption of "microorganisms formed by transferring certain kinds of well-defined genetic material from plant pests" be repealed. The scientific rationale for this exemption has been long and amply defended by USDA and the Biotechnology Science Coordinating Committee; the exemption, based on the NIH RAC long-standing principle of lesser regulation for organisms that result from self-cloning, is, in fact, extremely conservative, in the sense that a coherent argument can be made for a substantially broader exemption.

See comment 7.

7. The draft report fails to distinguish between authoritative sources and those that are not. For example, the NAS report (as well as those consistent with it) is given short shrift, while the Shackleton Point Workshop is overemphasized. Also, there are vague references to "scientific societies" views that are misrepresented out of context. Furthermore, the draft report looked at a scientific controversy, the ecologists "versus" the microbiologists, as exemplified by the March 13, 1987 Science articles by Sharples and Davis (see bibliography), and came down on the side of the ecologists. This leads to an overly

risk-averse public policy bias in the draft report. We suggest that the auditors read Davis's response to Sharples in the MBL Collecting Net, August 1987. To compound this problem, the report is less than rigorous in its presentation standards. This is most evident on pp. 108 and 109, where an unnamed "molecular biologist experienced in risk assessment" makes several assertions and reports "scientific estimates" (without citation) which are "questioned by Federal officials."

See comment 8

8. The GAO draft report omits critical discussion of the underlying risk assessment or management assumptions of EPA regulatory mechanisms. Generally, there seems a lack of appreciation of the complexities of risk management, which requires balancing the risks of not testing and approving new products as well as those for testing, and which involves more than just regulation. Specifically, in view of the broad consensus about the newest genetic engineering techniques representing only refinements of older ones, the draft report does not examine the scientific rationale for EPA's level of regulation. In fact, far from questioning the assumptions underlying EPA regulations, GAO calls for still further increased stringency by EPA (last sentence of Executive Summary).

See comment 9

9. Finally, the draft report is not adequately rigorous in identifying potential environmental hazards (pp. 19 ff). Certainly the Army did an exhaustive job in its Draft Environmental Impact Statement on the Biological Aerosol Test Facility at Dugway Proving Ground (January 1988). The draft report does not present any information on harmful introductions of microorganisms, nor on the necessary scale of such introductions, either for harmful effects or for long-term establishment. The issue of scale of field tests is generally not dealt with in detail in the draft report, but clearly will have an important part in decisions about likelihood for establishment and harm for a given introduction.

The following are GAO's comments on the Department of Health and Human Services' letter dated March 15, 1988.

GAO Comments

Rather than specifically referring to our review of FDA's risk management activities, HHS comments concern the definitions and assumptions underlying federal risk management of genetic engineering. The following responds to points made in the HHS letter.

1. To make clear to the reader what we mean by genetic engineering, we have added material to chapter 1 describing the distinction between the newest genetic technologies and traditional methods. It is widely recognized by scientists that the newest techniques, including rDNA, can produce combinations of properties that are not achievable by older methods of genetic manipulation, such as plant hybridization and animal breeding. As noted in the National Academy of Sciences (NAS) paper, "The power of R-DNA techniques lies in their ability to . . . overcome the barriers of sexual incompatibility that have hitherto stymied breeders' efforts to move genes." Further evidence of this distinction is the fact that the NIH RAC was established in the mid-1970s to oversee rDNA research. Therefore, our use of the term appropriately applies to those methods of genetic manipulation developed since that time.

2. We recognize that conventionally produced products, such as live viral vaccines and microbial pesticides, have been used safely in humans and the environment for decades under federal regulation and nowhere in our report do we discount agency experience with these products. In fact, FDA's policies and procedures for reviewing applications to test new vaccines made by rDNA are no different from the regulations and review process employed by FDA in approving clinical investigations of conventionally produced vaccines. Furthermore, EPA's experience with microbial pesticides has led to efforts within the last several years to revise the testing guidelines and data requirements for pesticide registration (including genetically engineered microbial pesticides).

We believe, however, that the amount of agency experience relevant to managing the risks of introducing rDNA organisms into humans or the environment has been limited. Two types of comparisons can be made. First, since some products made by the new genetic techniques may be similar to those derived from conventional methods, regulatory experience with the former may indicate risk management approaches with the latter. Even in cases where the new product is virtually identical to the old, however, additional factors may also need to be considered in

the safety evaluation. For example, as noted in HHS' own policy statement in the Coordinated Framework, new or supplemental marketing applications will be required for most rDNA products under its jurisdiction. The rationale given for this position is that

"Because of potential differences in the products resulting from use of recombinant DNA technology, the resulting products may be 'new' products requiring separate approval under the applicable statutory provisions."

Another comparison is between experience with genetically engineered organisms in containment and in the environment. Until recently, organisms made by rDNA techniques have been used only in containment. As the report points out, rDNA organisms have been used extensively in laboratories and fermentors for the production of pharmaceutical and other products. For such uses, the organisms are contained physically and limited biologically so that they are unable to survive and reproduce outside containment. Such experience, however, is not comparable to releasing genetically engineered organisms designed to survive and function in the environment. The latter involves the organism's interaction with a large number of ecological factors that determine its behavior and therefore the impact on the environment.

3. In chapter 1, the report emphasizes the importance of focusing on the risks of new organisms rather than the fact that their newness resulted from the application of genetic engineering technology. We quote the NAS paper referenced in HHS' comments to emphasize the importance of evaluating the nature and behavior of the product, and not the process by which it was developed. We state that the critical perspective for assessing risk is to examine the interaction of the genetically engineered organism with the environment to which it is introduced.

In practice, however, it is not clear that agencies have been consistent in adopting this principle in developing their regulations for genetically engineered organisms. This point is open to interpretation. Some scientists have characterized EPA's definition of a "new" microorganism under TSCA (formed by combining genetic material from dissimilar sources) as a process-based definition. Likewise, USDA's exemption for transfers of genetic regulatory sequences could be seen as emphasizing process over product. Any inconsistency in applying the "product over process" approach to specific agency regulations may reflect more the current regulatory framework rather than any misplaced emphasis by GAO.

4. The literature that we examined in the course of this review does not support HHS' position. Rather, scientists and regulators have emphasized the need to improve methods for assessing potential effects of releasing genetically engineered organisms into the environment. Our report reflects their concern about the adequacy of predictive risk assessment models. In chapter 1, we discuss the analytical framework and the state of knowledge available to predict the behavior of an organism new to an environment. In chapter 2, the step-by-step approach, which HHS supports, is described as a valid and appropriate approach to developing data necessary for predicting the behavior of genetically engineered organisms in the environment. We also note that while predictive capacity is limited at present, the relevant data base can be expanded and uncertainty reduced through field trials properly designed to test the genetically engineered organism's safety and efficacy.

5. While exempting categories of products from regulatory scrutiny may be an appropriate goal for federal agencies, the Organization for Economic Cooperation and Development recommendations also state that it is necessary to evaluate risk prior to releases into the environment and that it is premature to develop general guidelines. In order to develop criteria or general guidelines for exemption, we believe that a record of relevant experience must first be gained. As stated in chapter 2, an appropriate model for regulating environmental releases is the process followed by the NIH-RAC. This approach began with comprehensive, "every case" coverage. As experience was accumulated, classes of experiments were recognized as safe and so could be exempted from oversight. Generic criteria for exempting certain environmental releases from review will require a history of cases that is not yet available.

If relevant experience or data indicate that certain genetically engineered organisms warrant exemption, USDA and EPA can use regulatory mechanisms under existing statutes to waive requirements for reviewing them. Until that time, the agencies could establish a system (such as that set up by EPA under FIFRA) for applying varied levels of scrutiny based on anticipated levels of risk. Establishment of a "triage" review process would allow agencies to allocate more resources to evaluating products considered to be of higher risk, while not relinquishing regulatory control over field testing organisms categorized as being lower risk.

6. As shown in chapter 2, we support the NIH-RAC process of developing exemptions from federal oversight of laboratory rDNA research, but we do not believe that specific exemptions resulting from that process necessarily apply to environmental releases. Our recommendations to USDA

and EPA are based, in part, on their deviation from the NIH-RAC approach to developing experience-based exemptions from review. In particular, the NIH-RAC exemptions for organisms used in contained facilities resulted from a significant amount of relevant experience with organisms in containment. In contrast, USDA and EPA policies differ from this approach in that they exempt certain genetically engineered organisms to be used in the environment before establishing a record of experience with such organisms in the environment.

As for the HHS criticism of our recommendation to USDA, we have discussed this in chapter 2 in our response to USDA's comments.

7. As shown in appendix III, our report reflects the views of scientists from a broad range of disciplines. Many of the documents cited in the HHS comments, including the NAS paper, were used in preparing this report. However, we find that these same sources present a more balanced and cautious perspective than that advocated by HHS. Further, the NAS paper's ecological perspective was provided by the Director of the Cornell University Ecosystems Research Center, a sponsor of the Shackelton Point workshop that HHS believes we overemphasized.

Moreover, we believe HHS' comment misrepresents the scientific debate. The dispute properly seen is between molecular biologists and ecologists, with microbiologists appearing in both camps. In our review of the scientific literature, we found that the two opposing groups present very different sets of evidence. The challenge to regulatory agencies is discerning the relevance of the evidence to the issue of field testing genetically engineered organisms.

We also take exception to HHS' charge of bias. Our conclusions are based on the view that the potential risks associated with introductions of genetically engineered organisms are uncertain and that more environmental research is necessary. The premise underlying our analysis is that agencies need to design policies and procedures to decrease the uncertainty and increase the data base on environmental introductions. To do this, federal risk managers should adhere to the following guidelines: (1) conduct prerelease reviews of laboratory data and testing protocols using evaluators with appropriate scientific expertise, (2) ensure that the agency has the ability to prevent a planned release if it determines that the risks of field testing are unacceptable, and (3) develop policies and procedures so that agency resources are allocated to areas of greatest need for oversight and that regulation evolves with advances

in scientific knowledge. In our view, this approach will facilitate the prudent development of a promising technology.

8. Our scope, as defined by the requester, was to examine agency policies, administrative procedures, and technical methods for risk management of environmental releases of genetically engineered organisms. This is stated explicitly in the "Objective, Scope, and Methodology" section in chapter 1. In addition, in chapter 3 we discuss each agency's review process and decision-making criteria, including the use of risk-balancing analysis.

The assumption underlying EPA's policy is that field tests of genetically engineered organisms will vary in their potential risk. The agency's risk management policy, which we endorse, is that some, if not the same, level of regulatory scrutiny be given to all proposals for environmental release. The establishment of more and less intense levels on review for high and low risk categories is supported by scientists with various perspectives on the risks of environmental introductions. Our recommendation to EPA reflects the inconsistency we found between its policy statement and proposed procedures outlined by the agency in the Coordinated Framework.

9. A detailed identification of potential environmental hazards was outside the scope of our review, but is briefly outlined in the introductory chapter. Likewise, the relevance of scale is mentioned in chapter 1 as one of the important considerations in assessing the risks of environmental releases. Scientific issues surrounding environmental releases are addressed in a 1988 report by the Office of Technology Assessment entitled New Developments in Biotechnology—Field-Testing Engineered Organisms: Genetic and Ecological Issues.

Major Contributors to This Report

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